DRAFT

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Comments on CMS Clinical Research Policy
(Comments are made by representatives from Institutes and Centers across NIH in response to the 10 questions)

1. Clarify payment criteria for clinical costs in research studies other than clinical trials.

The current criteria for routine costs in clinical trials would be appropriate for other clinical research studies that are not interventional.

Research questions of relevance to beneficiaries can be answered in clinical studies that are not clinical trials. Clinical services needed to address questions of relevance to Medicare beneficiaries are appropriate for CMS reimbursement.

The multiple paragraph regarding criteria and desired characteristics should be combined and streamlined for clearer picture of which trials are qualified.

The prevention issue is quite important and needs to be discussed. CMS can pay for care related to a disease but not to prevent development of a disease. This is one of the reasons why there was a debate about whether obesity was a disease and whether participation in weight loss programs could be covered by Medicare. (see: http://www.cms.hhs.gov/MLNMattersArticles/downloads/MM3502.pdf). Diabetes is another similar issue. CMS could not cover diabetes prevention since "impaired glucose tolerance" or "impaired fasting glucose" is not a disease. Coverage may be possible under the term "prediabetes". The same considerations apply to trying to get coverage of attempts to prevent hypertension.

There is a strong need to extend coverage of routine clinical care costs for studies beyond those covered by the current policy. For example, a quick review of the treatment of lumbar stenosis, a common, disabling condition in the elderly, finds no definitive trials of different management strategies and no clinical consensus on appropriate treatment. Large scale clinical studies are needed, and can only be accomplished with CMS coverage of routine clinical care costs. Observational cohort studies may be necessary prior to RCTs to design appropriate trials.

Clarification is particularly needed for circumstances (if any) that justify coverage for routine costs associated with studies that are NOT directly evaluating effectiveness (i.e., observational studies).

2. Devise a strategy to ensure that Medicare covered clinical studies are enrolled in the National Institute of Health (NIH) clinical trials registry website.

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There is currently increased pressure on the sponsors for registration of their clinical trial in ClinicalTrials.gov regardless of the source of funding. A policy adopted by the International Committee of Medical Journal Editors (ICMJE) that went into effect for all new trials starting in September 2005, requires trial registration prior to enrollment in order for study results to be considered for publication in member journals such as the *Journal of the American Medical Association* or the *New England Journal of Medicine*. Legislation backed by Senators Charles Grassley (R-Iowa) and Chris Dodd (D-Conn) proposes fines for study sponsors that fail to register most clinical trials for medical devices as well as drugs and biologics. Thus, a requirement to have a trial registered in ClinicalTrials.Gov regardless of their source of funding should definitely become part of the policy. This requirement could be enforced through including the ClinicalTrials.gov Identifier on all reimbursement requests submitted to the CMS for each participant enrolled in a clinical trial. At present, there are no requirements for clinical studies that do not involve an intervention to be registered in ClinicalTrials.gov, and there are no pending plans to establish a registry for such studies. Registration of such studies in ClinicalTrials.gov is not desirable because it could cause confusion among prospective participants as to the nature of the study and its risks and benefits to the participants. Thus, while registration of the clinical trial should be a requirement for providing coverage for the routine costs, such a requirement for clinical studies without an intervention is not feasible.

Enrollment in a data base is largely already required by NIH and journals for clinical trials and can be made a requirement of any study seeking CMS sponsorship. Excellent use of an already existing system already required by publicly funded trials/studies.

3. Develop criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries, by demographic and clinical characteristics.

Please clarify, "Develop criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries by demographic and clinical characteristics". Such a requirement, if hard and fast across all studies, would be counterproductive. It is recommended that standard desirable "Medicare" demographics be provided and that the target population be tailored by each study and be consistent with the disease or condition being evaluated/treated and existing federal policies regarding inclusion of research subjects. The appropriateness of the target study population is an important research question that is integral to peer review and contributes to the determination of scientific merit. Would peer review assessment of the proposed study population be used to judge this policy?

NIH and other federally funded studies have to demonstrate appropriate target enrollments of women, children and minorities underrepresented in research and/or justify why if they are not included as participants in a research study. We believe that similar standards should be applied to any Medicare covered clinical research study.

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Target enrollment forms and enrollment justification should be required of other studies as part of the qualifying process for coverage. The "NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001" could serve as a template for the development of such criteria by the CMS could serve as a template for the development of such criteria by the CMS. (http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm)

Compliance with the NIH policy is ensured as part of the peer review process for NIH funded clinical studies but it is unclear how similar requirements could be enforced by the CMS for clinical studies with sources of funding other than the NIH. It should also be noted that if the CMS establishes criteria quite different from those adopted by NIH, the NIH-funded studies will also need to go through the same review process by the CMS to verify that they meet the reimbursement requirements.

Understandably, CMS wants to be sure that it is only paying for clinical services related to questions relevant to its beneficiaries. However, limiting trials to having certain numbers of Medicare beneficiaries may preclude conduct of a trial with enough power to answer the question. Examples might include treatments for breast cancer or revascularization in diabetics. The criterion should be: will the results of this study help Medicare beneficiaries not whether Medicare beneficiaries or similar patients are included in the trial. CMS should set criteria establishing relevance to the Medicare population. In large studies, CMS can require that analysis include stratification by age in order to look for differential effects. How would this be managed if the "oversight board is not being implemented and is it worth the resources? Studies that include those who are eligible for Medicare services are a different research population in general. Typical studies will include adults up to age 65.

Current NIH policy requires that investigators specify plans to include a representative sample of the population, including gender and minorities, except where there are valid scientific justifications for a non-representative sample, e.g., conditions that do not occur in some groups.

NIH would prefer that this be a guideline, not a criterion. It is not clear if this is possible to do in advance of each research study. Although this is a laudable goal, it is doubtful that strict criteria can be developed. This would also eliminate participation of Medicare recipients in small phase I and phase II studies since these are usually small and not feasible to ensure demographic and clinical characteristics of study participants. (NIH only has the representative requirement for large phase III studies.)

4. Clarify the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials.

The current definitions of routine clinical care costs and investigational costs seem to be satisfactory. However, the third exception to the coverage states that "Items and services customarily provided by the research sponsors free of charge for any enrollee in the trial" are excluded from the coverage. Usually, all study related measurements and procedures

(e.g., physical examination, routine laboratory tests, etc.) are provided free of charge to the participants and paid by the sponsors. At the same time, most of these items and services (with some exceptions) are part of routine clinical care for a patient with a disease that is under study. Thus, more direct and easily understandable language needs to be provided to resolve this confusion. A list of specific covered procedures for clinical research studies would be the least ambiguous approach.

In clinical research, investigators have an obligation to the participant to monitor safety closely and evaluate outcomes fully. Collecting an incomplete set of outcomes would be just as unethical as not monitoring safety. Thus, routine clinical care costs in a clinical study are more frequent and extensive than needed for diagnosis and treatment of a complaint. In this era of personalized medicine, extensive collection of outcome data allows investigators to determine the phenotypic characteristics of patients most likely to benefit from the intervention.

Please see draft guidance by OHRP on Definitions of clinical research so the definitions are consistent against Federal agencies.

Double dipping by seeking research funding for an aspect of care such as a procedure or visit that might be considered routine but is integral to the research question is an important source of concern for investigators and those charged with oversight. Clear guidance and methods to achieve acceptable, accurate billing would be helpful.

A key issue is the definition of routine clinical care. In some instances, such as when the trial involves the evaluation of a new device, the ordinary clinical care is quite clear and the policy has worked OK on several trials. When the trial tests new uses of already approved therapies, the boundaries between clinical care and research become indistinct. One example illustrates this problem that has occurred in multiple studies. When a trial was designed, the costs were estimated based on the increased effort required to achieve intensified diabetes care, with treatment of glucose, blood pressure and lipid levels to the guideline recommended targets in the control group and the research target in the intervention group. These estimates were based on discussions with several clinical trials experts. When the contract proposals were received, the costs had increased substantially. (This was one of several factors that drove up the actual cost of doing the trial.) It turns out that routine care controls hemoglobin, blood pressure and lipids at levels substantially above recognized guidelines. Investigators explained that their business offices would not allow them to bill for the control to guidelines for fear of insurers or Medicare requiring major retroactive payments for using clinical funds for research at some time in the future and the NIH then refusing to come up with the added costs. Clear definitions are necessary and the details need to be worked out in a general policy statement that facilitates getting future trials up and going without long delays while negotiations are going on for individual studies or even parts of studies.

An additional problem arises from the requirement for a copay by Medicare beneficiaries whenever they receive a covered service. Since patients find it very difficult to understand how they as being asked to "pay" when they participate in clinical research,

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the research project ends up having to cover this cost in some way. Recruitment is often difficult and this issue imposes an additional impediment to getting patients into a trial, with the strongest disincentives falling upon those with no supplemental coverage - often the poor and minority populations. Both Medicare (by getting more information for evidence-based medical decisions) and the NIH, by being able to do additional trials with our budget, would benefit from an exemption from this requirement for those participating in clinical trials.

Many NIH protocols state that the sponsor will pay for the cost of services in the event that the patient's insurance does not. In this situation, CMS automatically considers the sponsor (i.e., the NIH) as the primary payer for these clinical research services. NIH trials end up paying for costs of enrolling Medicare patients when this should be covered by CMS. CMS should automatically cover Medicare patients in deemed clinical trials if they do not have any private insurance. This would lead to many more Medicare patients being enrolled in NIH trials and would save the NIH from paying these enormous patient care costs.

There should be more transparency with regard to how to apply for such coverage of routine clinical costs in a trial. Are there defined criteria for CMS review of proposals and a timeline for CMS to respond when a proposal is submitted? Information on who to contact in CMS would also be helpful. If someone is getting care in the context of a trial, specific guidance is needed with regard to billing. Often visits involve both collection of data and patient management. When the two are done jointly by a trial coordinator can a patient care visit charge be reimbursed? What if the patient belongs to an HMO and the trial is not being done through the HMO, can patient care costs be recovered if the HMO is also getting funded to provide overall patient care?

Clarification is particularly needed as to how the term "investigational" refers to items/services that are being covered outside the qualified clinical trial [e.g., coverage for surgical or other procedure that is covered outside of the study despite lack of clinical trial evidence of efficacy]

5. Remove the self-certification process that was never implemented.

Generally all medical research meets the self-certification criteria, thus they are redundant. Even though an individual participant may not benefit from participating in the study, it is expected that the results will benefit the public. The self-certification process should be removed.

6. Clarify the scientific and technical roles of Federal agencies in overseeing IND Exempt trials.

This is a far reaching issue that may take years to resolve, if requirements for the scientific and technical oversight of the clinical trials need to be harmonized across the Federal agencies supporting clinical trials. In terms of the scientific and technical oversight, the NIA treats the IND Exempt clinical trials no differently from those trials

conducted under the IND. Depending upon the funding mechanism (R01 or U01), involvement of the NIA can vary from usual grant stewardship to significant scientific involvement in protocol development, study implementation and data analyses. NIH investigators are required to have a protocol. Then they need to meet the IND regulatory requirements by either securing the IND with the FDA or obtaining the IND exemption from the Agency, and there must be appropriate safety oversight mechanism in place (either DSMB or a Safety Officer) commensurate with the trial size, level of risk to the participants and trial complexity. Thus, while clarification of the scientific and technical role of the Federal agencies in overseeing the IND Exempt trials in the Policy is highly desirable, lack of such clarification at this time should not affect the reimbursement of routine clinical care costs in clinical research studies by the CMS.

NIH has an obligation to ensure that all the clinical studies that it sponsors ask important questions, are well-designed and feasible, and meet safety and ethical standards, regardless of whether the study meets the criteria for having an IND or not. Each of the federal agencies similarly has a mission that defines its role in the conduct of a study. Could this eligibility be managed or overseen by Medicare choice institutes with an IRB, or a central type board already reviewing the study for coverage of costs.

Agree in principle, but not sure what the problem is. As with item 3 above, can this be done in advance of each study? Should this be done on a case by case basis? All NIH funded clinical studies require peer review and oversight by program staff. The degree of oversight is contingent on the complexity and risk of the study, appropriately.

7. Determine if coverage of routine clinical care costs is warranted for studies beyond those covered by the current policy.

This is very important. I think that NIH would prefer a more liberal definition

Studies that are NOT directly evaluating effectiveness (i.e., observational studies) should be included.

Yes, if it promotes the health of this population or leads to increased knowledge it should be supported within the guidelines of covered items/test, etc.

One of the three requirements that the trial must meet to qualify for Medicare coverage indicates that "Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers." This requirement excludes all clinical trials where prevention of a disease rather than its treatment is a goal. Patients enrolled in these trials may not have a diagnosed disease at the time of enrollment, but by commonly recognized criteria, they have a high risk of developing such a disease in the future. Thus, coverage of routine clinical care costs in prevention clinical trials should also be provided.

In the current scientific environment of expanding technology and molecular knowledge, most epidemiologic studies (including surveys) require medical information and records, basic and specialized laboratory studies, and collecting biological specimens for

reposition. In addition, many include functional and performance-based assessments. As the older population increases, and issues related to general health, functional status and independence, living situations and social and financial support become more relevant to health expenditures, this type of research becomes more important in determining current and long-term needs. Special requirements of this type of research are quite different from those of clinical trials, and this area of research participation needs special attention and consideration with regard to CMS coverage.

Certain items and services are of benefit to Medicare beneficiaries, but are not covered for lack of a benefit category. Pulmonary rehabilitation and nutritional counseling are examples. While these items and services can sometimes be covered as part of another service, this ties coverage to the other service, which may or may not be appropriate. CMS should create a special, temporary benefit category for these services while under study. In order to obtain answers to questions relevant to Medicare beneficiaries or to determine which Medicare beneficiaries will benefit, it may be necessary to pay for clinical services that monitor a full range of outcomes of the service in detail.

8. Clarify how items/services that do not meet the requirements of 1862(a)(1)(A) but are of potential benefit can be covered in clinical research studies as an outcome of the National Coverage Determination process.

Part of NIH's mission is to facilitate translation of research findings it has supported into practice. For CMS to reimburse for new items/services, it must have evidence to support coverage as reasonable and necessary. NIH and CMS have cooperated before in collection of data to determine efficacy and if coverage were reasonable and necessary, each according to its own mission. These highly successful collaborations can serve as models for future collaborations by which NIH facilitates the translation of findings into practice and CMS collects the evidence it needs to make a NCD. Regular exchange of information on items/service under consideration for a NCD is necessary to coordinate the processes in both agencies.

Patients at high risk for poor outcomes are often poor, without insurance, or underinsured. These patients are often excluded from clinical trials because of costs and certainly hamper efforts to reduce health disparities. Extending the policy to include patients with no insurance and those with Medicaid would facilitate appropriate inclusion of important under-served groups in research studies

CMS currently deems all trials funded by federal agencies or conducted under FDA IND applications as qualified. The Guidance Section VI (B) would expand the range of trials substantially, and could present a substantial burden on CMS to review clinical trials. Given the stringent funding constraints on NIH institutes over the foreseeable future, it is likely that many high quality NIH applications for clinical trials will not be funded. In this situation, it may be desirable for CMS to deem all NIH applications receiving a priority score in the Outstanding or Excellent categories as qualified. In this way, NIH applications that are well-designed trials but fail to receive NIH funding may proceed

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with research funding from other sources. This may decrease the burden on CMS staff to review clinical trials.

The design of the clinical study should be appropriate to the research question, as specified in the proposed guidance. Thus, the issue of whether other research studies, e.g., quasi-experimental, observational, or un-blinded studies, should be deemed qualified does not need to be answered separately. An application receiving high marks from an expert review group should be deemed qualified, independent of the type of study design. Thus, payment for clinical costs in research other than randomized clinical trials can be accommodated on the basis of the study quality. Typically, the review criteria include: Significance, Originality, Research Plan, Qualifications of the Investigator(s), Research Environment, and Inclusion of Women and Minorities.

9. Clarify whether and under what conditions an item/service non-covered nationally may be covered in the context of clinical research to elucidate the impact of the item or service on health outcomes in Medicare beneficiaries.

The first exception to coverage states that "The investigational item or service, itself" is not covered. However, there is a great interest in "comparative" clinical trials testing efficacy of one intervention (or drug) in comparison to some other intervention (or drug). In NIH-funded clinical trials, many such drugs and intervention are marketed products and are also covered by the CMS. However, when they become the "investigational item or service", by definition they are excluded from coverage, but should be covered. Comparative trials could be an efficient process for the CMS in determining what services and drugs to cover.

In general, an item or service not typically covered should be covered if the item or service, as a result of a clinical research study, could be shown to have a potential impact on health outcomes or could become a more cost-effective treatment alternative. If an item/service is a critical part of the protocol, a critical intervention, or could potentially alter the outcome of the primary intervention under study, it should be covered.

There is a concern that covering services/items that are already acceptable would allow the sponsor of the trials to cover these non-covered expenses. It might be seen as coercive if services are covered under a clinical trial but not under normal conditions.

Service or items that are non-covered nationally could be covered in the context of clinical research if there are adequate pilot data and an appropriate study design sufficient to convince an independent review group of the value of the study.

Clarification is particularly needed with regard to surgical interventions or other treatments that are unlikely to be supported by industry or other sponsors

10. Discuss Medicare policy for payment of humanitarian use device (HUD) costs.

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A Humanitarian Use Device is a medical device intended to treat or diagnose a disease or condition that affects, or is manifest in, fewer than 4,000 individuals per year in the United States. The HUDs should be covered when they are used in clinical research studies with prospective data collection. Such studies should be conducted under a research protocol, be in compliance with the informed consent and IRB oversight requirements, and one of the Federal agencies (e.g., FDA, NIH, VA, etc.) should be in charge of overseeing such studies.

There should be more discussion / cooperation between the FDA, CMS, and NIH on the impact of FDA approval of devices under an HDE. Often this leads to these devices becoming part of the "standard of care", especially if CMS decides to cover the costs of these devices and services, which makes it virtually impossible to recruit patients for a Phase III trial to evaluate the effectiveness of the device. CMS should only cover patients undergoing procedures using a HDE device who are enrolled in a deemed randomized trial. National Coverage without this restriction would make it virtually impossible to carry out a randomized trial comparing involving an HDE device because the financial incentive to provide such a device would severely limit enrollment in a trial. With this scenario, use of the device could become widespread without evidence of its relative efficacy and safety.

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CMS clinical trials policy
Comments from the OD/OSP Clinical Research Policy Analysis and Coordination Program (CRpac)
(Dr. Amy Patterson, OD/NIH)

Some questions and issues for consideration

1. Clinical trials conducted or supported by NIH are, by definition, qualified to receive CMS support for routine care, as required by the CMS 2000 Clinical Trials Policy,[1] but they must have therapeutic intent. Some trials may be primarily designed for safety endpoints but also measure efficacy, but without sufficient statistical power to draw conclusions regarding efficacy. Would these trials be considered to have therapeutic intent?

2. Should the CMS clinical trials policy could be broadened to cover other trials, e.g. routine care in early phase studies?

3. The definition of routine care may be challenging.

    a. There may be routine clinical procedures that are not covered because they are non-covered procedures; other clinical trial procedures that are also considered routine can be covered as long as they would have been conducted in the same patients absent the clinical trial. However, if there is an extra lab or follow-up test or a more intensive monitoring protocol, it may not be clear exactly where the boundary lies. Also, routine care varies significantly by provider, hospital or clinic, and region. So what portion of a clinical trial protocol is considered "routine" may vary at different sites in a trial. Is it desirable to standardize the reimbursement across multi-site protocols? If so, how can this be accomplished?
    b. For some diseases or disorders there is no standard established effective treatment, e.g, some advanced cancers. Different providers may use different approaches based on their best estimate of what might hold some promise for amelioration of disease; would any of these be considered routine care? How would these determinations be made?

4. The clinical trials policy excludes "items or services customarily provided by the sponsor free of charge." This exclusion needs clarification. Different items or services might be provided in some trials and not others, or by some, but not all, sponsors.

[1] The NCD on clinical trials coverage defines four criteria for coverage: a) the trial must be studying an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment); b) the clinical trial must have "therapeutic intent;" c) the trial must enroll patients with diagnosed disease; and d) the trial must be qualified by virtue of its sponsorship by a federal agency or status vis-à-vis FDA regulations.

5. The overall uncertainty about what services are covered affects the planning stage for clinical trials, and makes it difficult for the sponsoring institute to know what the budget implications will be. If coverage expectations turn out to be unrealistic, budget shortfalls could occur, or patients and providers could be left with unreasonable costs.

6. The billing procedures can be confusing. Sometime it may not be clear whether a given procedure is considered routine care, or not. In research studies that involve coverage with evidence development as well as coverage of routine care, the billing procedure for routine versus experimental procedures would be different—but it is not always clear in a trial where this boundary lies.

7. In surgery or other areas with evolving practice, when is a new procedure considered experimental, and when it is considered a variation on standard practice? For example, carotid stenting is an area of ongoing investigation and evolving clinical practice. A process of negotiation was set up among specialty societies and CMS in order to define acceptable practice and determine reimbursement policies.[2]

8. What about off label use of drugs? When is off-label use considered validated medical practice, from CMS' point of view? Again, there may be evolving medical practice in which approved drugs are used for different indications or in different patient populations; at what point is such practice considered routine care? How would these determinations be made?

9. Achieving a representative sample of older persons may be difficult in many trials. The concept of trials with representative populations is a laudable one, but strict requirements for accrual of representative Medicare populations may be very difficult to meet, and also may conflict with NIH's existing requirements regarding inclusion of women and minorities in clinical research. The most important question from the point of view of CMS decision making might be the inclusion of the kinds of patients who will be likely to receive the intervention being studied—which would likely be a subset of the entire Medicare population.

10. CMS' policy on secondary payments may complicate issues regarding whether a research sponsor or CMS is responsible for payment. CMS' secondary payment policy states that CMS is not responsible for paying for services that are covered by another payor. If a research sponsor agrees to pay for any services that are not covered, this could effectively leave the sponsor responsible for all services as the primary payor, since CMS' secondary coverage rule would apply.[3]

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[2] Zwola RM. Reimbursement for Carotid Stenting: Unique Challenges for Medical Centers and Physicians. Sem Vascular Surgery 2006;19:87-91.

[3] Barnes M and J Korn. Medicare Reimbursement for Clinical Trial Services: Understanding Medicare Coverage in Establishing a Clinical Trial Budget. J. Health Law, Fall 2005.

11. There may be substantial motivation for device companies to solicit CMS payment for care received in device trials, which may involve surgical implantation. These trials may be costly, and this may use up significant amounts of CMS funding. Therefore, it might be appropriate to suggest that CMS introduce a mechanism for vetting of coverage of clinical trials care that includes weighing the public health importance of the topic of the research.

12. The CMS policy requires that clinical trials receiving CMS coverage must be registered with the NIH database, ClinicalTrials.gov. If the clinical trials policy is now expanded to include observational studies, these studies would need to be registered as well. While the majority of studies on ClinicalTrials.gov are, in fact, interventional studies, and the registration of observational studies is not required by law, ClinicalTrials.gov does accommodate and encourage the submission of observational studies, such as NHLBI's Framingham Heart Study (http://clinicaltrials.gov/ct/show/NCT00005121). This capability is built into the ClinicalTrials.gov standard data elements (http://prsinfo.clinicaltrials.gov/definitions.html), including Study Type (i.e., "Observational") and Study Design (e.g., Purpose: "Natural History," "Screening," and "Psychosocial"). At present, ClinicalTrials.gov currently contains over 4,700 observational studies (of over 32,000 registrations).

13. Given the importance of CMS Clinical Research policy, as well as the CMS policy on Coverage with Evidence Development, and given NIH's role in conducting a large share of publicly funded research, we recommend that a standing NIH-CMS committee work together on further development of guidance and policy on both Clinical Research Policy and CED.

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RE: NCD CAG-00071R

Dear Dr. McClellan:

The University of Colorado Cancer Center (UCCC) is the NCI designated comprehensive cancer center serving Colorado and the Rocky Mountain West. We appreciate CMS's willingness to address a number of issues that have surfaced since the issuance of the national coverage decision (NCD) on clinical trials. The importance of these rules extends beyond the Medicare program, as many payers look to Medicare when establishing their own payment criteria, particularly for items and services that may not be included as part of traditional insurance coverage. The UCCC comments have been submitted via the CMS website. This letter is being sent to ensure that you are aware of them.

The UCCC supports the three overarching goals identified by CMS and hopes that, in addition, the revisions to the Clinical Research Policy will provide consistency, clarity, and flexibility that minimize the risk that researchers and their institutions will be subjected to investigations and second-guessing when bills are submitted to Medicare for items and services provided to beneficiaries enrolled in clinical trials. Below are comments on a number of issues that were identified by the CMS Tracking Sheet as well as suggestions for additional issues to be included when the revised NCD is published.

1. Develop a strategy to ensure that Medicare covered clinical studies are enrolled in the NIH clinical trials registry website

The UCCC supports the development of such a strategy and urges CMS to work with NIH to ensure a reasonable process for enrolling studies in the existing clinical trials registry website. The UCCC encourages CMS to determine whether it also is appropriate to recognize trial registration in other sites. The registration requirement

should apply only for Phase II and III and later trials. While registration of Phase I trials should not be required, it is appropriate that, at a minimum, Phase I trials with therapeutic intent should be included under the Medicare coverage policy. Studies that are "exploratory" or "hypothesis generating" should be excluded.

Implementation of this strategy will require CMS to define "clinical studies." One possibility is:

> In addition to clinical trials, studies that collect data by various means (e.g., patient registries) in order to evaluate the efficacy and cost effectiveness of items and services to determine whether they should be covered by Medicare.

2. Develop criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries, by demographic and clinical characteristics

Having a "representative sample of Medicare beneficiaries" should not be a requirement of the NCD as it is a criterion that will be virtually impossible to meet in all instances.

Federal regulations already impose numerous requirements for human subjects research, including that the institutional review board (IRB) must ensure that the selection of subjects is equitable:

> In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. (45 CFR section 46.111(a)(3))

CMS should not impose any additional and possibly conflicting requirements that could affect the design of studies and the ability to recruit participants.

As CMS is well aware, the older population already is underrepresented in research studies. Imposing this requirement will likely hinder CMS's overarching goal of "allowing Medicare beneficiaries to participate in research studies" since it will mean that even fewer studies will qualify for Medicare coverage, and thus even fewer Medicare beneficiaries will have access to them. Additionally, the requirement for a representative sample could be very problematic for multi-site studies since any individual site may not meet this standard even if it is met (or there has been a good faith effort to meet it) when all sites are considered in aggregate.

An alternative to requiring a representative sample would be for CMS to require that—as appropriate for the particular condition or disease being studied—there

must be a reasonable process for making good faith attempts to recruit diverse Medicare beneficiaries. However, no study should be excluded from Medicare coverage because of the inability to recruit these individuals.

Further, it is extremely important to ensure that researchers not be placed in the untenable position of learning that CMS has performed a retrospective evaluation of the study population and determined that because a representative sample of Medicare beneficiaries was not recruited, all payments made for services to beneficiaries in the study will be recouped. To encourage studies to enroll Medicare beneficiaries, there must be ample assurance that once a study has been deemed to qualify for Medicare coverage, that decision will not be reversed. Otherwise, this requirement will be seen as an insurmountable barrier to encouraging Medicare beneficiaries to enroll in clinical trials.

3. Clarify the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials

Defining what is encompassed by the term "routine costs" has been a challenge since the issuance of the NCD. Most clinical researchers assume that "routine costs" means payment for what often is called the "standard of care." The UCCC urges CMS to adopt a policy that allows for flexibility in deciding which items and services qualify for Medicare payment. Eligibility for payment should be determined by asking the question: absent the clinical trial, would this physician treat this patient using this item or service? If yes, and if the item or service is not paid for by the sponsor as per the clinical trial agreement, then it should be paid for by Medicare.

Before a study begins, determinations should be made as to which costs are routine and which are not. However, CMS policy should allow for some deviation from these determinations when supported by a judgment that the particular item or service is medically necessary based on the condition of a specific patient. To adopt a more restrictive policy may have the unintended consequence of discouraging researchers from recruiting Medicare beneficiaries.

While CMS should not be in the position of determining what does and does not constitute routine costs, the agency should provide guidance about what is considered to be an acceptable process for making these decisions.

Finally, we request assurance that Medicare will not deny payment for all services to a patient if it is determined that some portion of the services do not meet the definition of "routine costs."

4. Remove the self-certification process that was never implemented

The UCCC supports the removal of the self-certification process, but urges CMS to adopt a process that allows for institutional certification so that Medicare coverage

can extend to trials other than those that that are "deemed." In 2000, AHRQ held two public hearings to gather comments about which trials other than those that are "deemed" should qualify for Medicare coverage, yet the agency never issued any guidance. It may be appropriate for the agency to do so now.

5. Clarify the scientific and technical roles of federal agencies in overseeing IND
Exempt trials

This area has traditionally been under the aegis of the Food and Drug Administration (FDA) and should remain there. CMS's role should continue to be that of payer and not overseer of any trials.

6. Determine if coverage of routine clinical care costs is warranted for studies beyond those covered by the current policy

As was discussed in #4 above, the UCCC supports Medicare coverage for studies beyond those currently covered. Generally, Phase I studies are paid for by manufacturers, so in many cases the items and services would not be eligible for Medicare coverage. However, in some Phase I studies—particularly cancer studies—this may not be true. As long as the study has a therapeutic intent, then it should be eligible for Medicare coverage, regardless of whether it is Phase I, II, or III. CMS should recognize that in some cases even studies that establish baseline levels or monitor toxicity absent signs or symptoms may have "therapeutic intent" and therefore should be eligible for Medicare coverage.

It has become clear to the research community that determining whether a study has therapeutic intent is key to deciding if enrollees in that study will be covered by Medicare. We are aware that CMS stated in a FAQ that "'the phrase 'therapeutic intent' is open to interpretation." (AHLA Audioconference: February 22, 2006; "Legal Issues in Medicare Reimbursement of Clinical Trials", CMS Response 2). As is often true, the need for certainty must be balanced with the need for flexibility. Therefore, UCCC suggests that to fulfill the "therapeutic intent" criteria, a reasonable requirement would be that institutions must have in place a consistent, articulated method for determining whether a study has therapeutic intent. Once an institution demonstrates that it has implemented and adhered to such a method to make a determination, CMS should accept its judgment that a particular study has therapeutic intent.

The UCCC also supports coverage of research studies that enroll patients who have not yet been diagnosed with a disease, but are at high risk of acquiring it because of family history and/or genetics. If CMS concludes that it does not have the statutory authority to cover such studies because they are considered to be preventive care, then we urge the agency to ask Congress for the necessary authority.

7. Clarify whether and under what conditions an item/service non-covered nationally may be covered in the context of clinical research to elucidate the impact of the item or service on health outcomes in Medicare beneficiaries

Any rules adopted to implement this policy should not be so rigid that they become a barrier to the rapid dissemination of new treatments and technologies. CMS already has begun to deal with this matter by approving coverage for specified new technologies that are conditioned upon clinical studies to evaluate efficacy and cost effectiveness. We applaud this effort and urge CMS to expand it.

8. Discuss Medicare policy for payment of humanitarian use device (HUD) costs

The UCCC supports Medicare payment for HUDs. Medicare payment policy should be consistent with rules and guidance issued by the FDA. For example, the recently issued Humanitarian Device Exemption (HDE) Regulations: Questions and Answers (July 18, 2006) state that:

- HUDS are for a condition or disease affecting fewer than 4000 individuals in the US per year;
- IRB approval must be obtained before a HUD is used, except in emergencies where the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient;
- The IRB should be responsible for initial as well as continuing review of the HUD;
- Off-label use of a HUD allowed in an emergency situation; and
- A HUD can be used for compassionate use

For Medicare payment purposes, the patient's medical record should contain documentation that the use of the HUD is medically necessary and that no alternative exists.

9. Other Issues

The UCCC requests that CMS also address the issues below when the final revision of the Clinical Research Policy is published.

a. Clarify application of the phrase "items and services customarily provided by the research sponsor free of charge to any enrollee in the trial"

The current NCD excludes coverage for "items and services customarily provided by the research sponsors free of charge for any enrollee in the trial". In the FAQ published following the February 22 AHLA Teleconference, CMS stated that "[t]he intent is to not have Medicare pay for services that are provided free to non-

Medicare participants." (CMS Response 6). The UCCC agrees with this clarification and asks that it be incorporated into the revised NCD.

b. Clarify policy for Medicare Advantage beneficiaries enrolled in research studies

Some UCCC members have reported that the policy in the current NCD regarding Medicare beneficiaries enrolled in HMOs is a disincentive for these individuals to enroll in clinical studies. The 2000 NCD says that for M+C (now Medicare Advantage) enrollees, contractors are to "pay providers directly on a fee for service basis for covered clinical trial services." The UCCC has learned that some contractors interpret this to mean that Medicare Advantage enrollees are responsible for co-pays at the same rate of 20% of charges that is paid by Medicare fee for service beneficiaries. However, many fee for service beneficiaries have insurance that covers these out-of-pocket costs, whereas most Medicare Advantage enrollees do not. Additionally, if Medicare Advantage enrollees have co-pays, the amount usually is substantially less than the fee for service co-pay.

Once a Medicare Advantage enrollee understands that he/she will be responsible for certain charges when enrolled in the research study, yet will not incur out-of-pocket costs for standard treatment, the enrollee often opts not to participate in the study. Not only does this limit access to these studies, but it imposes yet another barrier to recruiting Medicare beneficiaries. The UCCC requests that CMS adopt a policy that pays providers for "routine costs" of Medicare Advantage enrollees participating in research studies on a fee for service basis and does not allow contractors to impose co-pays or deductibles (other than amounts that must be paid by the beneficiary for any in plan service) on those individuals for those services.

c. Clarify relationship between "diagnostic intervention" and "therapeutic intent" requirement

Under 2000 NCD, a clinical trial must meet three initial requirements. The second requirement is that the trial must have "therapeutic intent." The third requirement states, in part, that "[t]rials of diagnostic intervention may enroll healthy patients in order to have a proper control group." Requiring a diagnostic intervention to have therapeutic intent appears to be contradictory. If CMS retains these criteria, the agency should clarify that a trial of a diagnostic intervention that often may not have therapeutic intent would be covered by the Medicare policy.

d. Screening tests/exams to determine eligibility for study participation

The UCCC suggests that the Medicare Clinical Research Policy should cover screening tests to determine eligibility for enrollment in a trial provided that these tests would be covered as part of the standard of care for a specific patient. All other screening tests should be charged to the study.

e. Allow Medicare payment for "compassionate use"

The UCCC requests that CMS allow coverage for enrollees enrolled in research studies when a physician has determined that there is no alternative treatment available and that the patient is likely to die without treatment ("compassionate use"). It seems unreasonable to deny Medicare payment for these treatments when no other options exist and the provision of the treatment may give researchers valuable information about treating future patients with the same disease or condition.

f. Application of the Medicare Secondary Payer rules

On July 19 the AAMC sent a letter to Steve Phurrough asking that CMS not adopt a narrow interpretation of the Medicare secondary payer (MSP) rules that would act as a barrier to Medicare payment for clinical trials. Should CMS not publish a policy on this issue prior to the issuance of the revised NCD, then the revisions to the NCD should include a clear statement of CMS policy about the impact of the MPS rules on Medicare payment for clinical trials.

Thank you for your consideration of these comments.

Sincerely,

Paul A. Bunn, Jr., MD
James Dudley Chair in Cancer Research,
Professor and Director, University of Colorado Cancer Center

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August 9, 2006

Submitted Electronically

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Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Department of Health and Human Services
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7500 Security Blvd.
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Re: Request for Comments on the Reconsideration of Medicare's Clinical Trial Policy (CAG-00071R)

Dear Dr. Fitterman:

We are pleased to respond to the Centers for Medicare & Medicaid Services' (CMS') request for public comment on the scope of its reconsideration of the clinical trial policy (now clinical research policy) national coverage determination (NCD).[1] Pfizer is a research-based organization with considerable experience in conducting and supporting clinical research. We are committed to improving both the transparency and accessibility of clinical research. We support CMS' goals to help Medicare beneficiaries find opportunities to participate in biomedical research and ensure that they receive the best care possible. We also support the broader evidence-based medicine movement and the development of information to support Medicare beneficiaries' healthcare decision making that is reflective of clinical judgment and individual patient values.

The reconsideration of Medicare's clinical research policy provides an opportunity to contribute perspective on ways in which clinical research can advance knowledge about treatments for diseases afflicting the Medicare population. In addition, we recognize that standards developed within this policy will affect CMS' revised coverage with evidence development (CED) guidance. We urge the Agency to discuss further the interaction between the clinical research policy and the

[1] Centers for Medicare & Medicaid Services. Reconsideration of Clinical Trial Policy NCD. Available at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=186. Issued July 10, 2006.

revised CED guidance. Pfizer welcomes this opportunity to assist CMS in clearly defining the scope of Medicare's clinical research policy; we plan to provide CMS with comments on the revised CED guidance document in a separate letter.

The following are recommendations on the scope of this NCD. In summary, as part of its reconsideration, we recommend that CMS should:

- Clarify the types of studies that qualify as Medicare covered clinical research;
- Clearly define what components of clinical research are eligible for Medicare coverage;
- Create an explicit process to determine the eligibility of particular clinical studies for Medicare coverage;
  Maintain flexibility for local contractors to cover the item or service under investigation for beneficiaries not enrolled or not eligible for CMS-approved clinical research;
- Grant timely and equal access to data generated from CMS-approved studies; and
- Clearly define CMS' involvement in the design of clinical research.

Recommendations on the Scope of the Clinical Research NCD

Clarify the types of studies that qualify as Medicare covered clinical research. CMS' existing policy defines a qualifying trial as that which evaluates a Medicare benefit, has a therapeutic intent, enrolls diagnosed beneficiaries, and has desirable characteristics. In the NCD reconsideration, CMS should further define the criteria for "qualifying research" and terms such as "therapeutic intent" and "desired characteristics" of clinical research.[2] For example, CMS should clarify which types of studies, including registries, observational studies, and practical/pragmatic clinical trials that will qualify for Medicare coverage. We believe that the qualifying criteria should include all types of research that are intended to evaluate a therapeutic intervention. In this regard, we would support the inclusion of Phase I clinical trials, if designed to test a hypothesis and any other hypothesis-testing, confirmatory clinical research studies. CMS should consider developing or adapting established criteria for covering routine cost of care in clinical research, such as those by the American Society of Clinical Oncology (ASCO).[3]

We also support CMS' continued efforts to convene an expert panel to define qualifying criteria. Although CMS is considering removing the self-certification process, we believe a more robust discussion is necessary. In addition to relevant Federal agencies, we urge the Agency to include manufacturer, provider, and patient groups on these panels and to open the meetings to the public to allow for broader input and transparency in the process.

Clearly define what components of clinical research are eligible for Medicare coverage under this policy. The final NCD should establish clear guidelines for research study sponsors on how they can work with CMS to ensure that appropriate provider and beneficiary expenses are

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[2] Centers for Medicare & Medicaid Services. NCD for Routine Costs in Clinical Trials. Available at http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=310.1&ncd_version=1&basket=ncd%3A310%2E1%3A1%3ARoutine+Costs+in+Clinical+Trials. Issued September 19, 2000.

[3] American Society of Clinical Oncology (ASCO). Coverage of Routine Patient Care Costs in Clinical Trials Position Statement. Available at: http://www.asco.org/asco/downloads/patient_care_costs_3.05.pdf. Approved March 2005.

covered during the study period. CMS' reconsideration of its clinical research NCD should define what is meant by "routine care" and "investigational research costs" suitable for Medicare payment in approved clinical research. CMS should also develop a process whereby the Agency works collaboratively with clinical research sponsors to determine payment responsibilities.

In addition, the Agency should address:

- *Application of Medicare Secondary Payer (MSP) Rules*: We encourage CMS to clarify that if a sponsor promises to pay for standard of care costs in clinical research not covered by another payer, it does not render the sponsor a primary plan under the MSP Rules. We do not believe Congress intended the MSP provisions to preclude Medicare from being a primary payer when a study sponsor promises to pay for uncovered clinical research services. However, if CMS determines that a sponsor may be considered an insurer under these circumstances, we suggest that CMS create a mechanism for determining which standard of care services Medicare covers.[4]

- *Medicare Payment for Investigational New Drugs (INDs) Charges Approved by the Food and Drug Administration (FDA)*: In approved Medicare clinical research, CMS should pay for INDs for which study sponsors have gained prior written FDA approval for charging research participants.[5]

Create an explicit process to determine the eligibility of particular clinical research studies for Medicare coverage. In order for the full benefit of this policy to be realized, CMS will need to define an explicit process that provides clarity and a level of predictability for the public and researchers to work with CMS. The NCD process could serve as a model for how this process can be established. The final NCD should clearly delineate the following:

- Whether CMS or another organization will determine what research qualifies for coverage of routine costs;
- What the decision-making process and criteria will be for CMS or another organization to conclude research is eligible for Medicare coverage, including what will constitute "routine costs" and "investigational costs in clinical research studies";
- How the public will be included in the decision-making process (e.g., comment periods, public meetings, etc.);
- What is the expected timeframe for making these determinations; and
- How CMS will evaluate the success of the revised clinical research policy.

Maintain flexibility for local contractors to cover the item or service under investigation for beneficiaries not enrolled or not eligible for CMS-approved clinical research. Beneficiaries who cannot participate in clinical research should be protected. Patients should not be denied

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[4] For additional information on the application of the Medicare secondary payer rule in clinical research, please see: Barnes, Mark and Jerald Korn. Medicare Reimbursement for Clinical Trial Services: Understanding Medicare Coverage in Establishing a Clinical Trial Budget. *Journal of Health Law*, Fall 2005. Available at: http://www.ropesgray.com/files/tbl_s20News/FileUpload116/1061/Article_Fall%202005_Journal%20of%20Health%20Law_Barnes_Korn.pdf.

[5] The FDA's policy for charging for INDs is governed by 21CFR312.7. Promotion and Charging for Investigational Drugs. Available at: http://www.fda.gov/cder/about/smallbiz/charging.htm.

Medicare coverage because their physician either does not participate in CMS data-collection efforts or cannot afford to participate or because they cannot participate in a clinical study. Therefore, we believe CMS should allow local contractors to cover beneficiaries who meet the study participation criteria, but cannot participate in clinical research due to circumstances beyond their control. In addition, local contractors should have the flexibility to cover beneficiaries whose provider refuses to participate in the CMS-approved clinical research. For example, CMS should allow local contractors to determine whether an item or service restricted to CED is medically necessary for the individual and have the latitude to extend coverage.

Grant timely and equal access to data generated from CMS-approved clinical research. In this NCD reconsideration, CMS should provide more detail on its intention to release the public data generated from CMS-approved clinical research, particularly research conducted as part of a CED decision. The public should have timely access to data, including Medicare claims for patients enrolled in CMS-approved clinical research and data generated through CED requirements.

In addition, CMS should clarify the type of access medical-product manufacturers will have to the data. In CMS' CED revised guidance document released July 12, 2006; CMS states that data generated through CED may "stimulate industry product development."[6] Yet, historically, CMS has not allowed direct access to CMS data if a medical-product manufacturer funds the study.[7] The National Institutes of Health (NIH) Data Sharing Policy creates a process that allows manufacturers to access data derived from clinical research on a study-by-study basis.[8] We encourage CMS to develop similar policies and processes for clinical research supported by CMS.

Clearly define CMS' involvement in the design of clinical research. In the reconsideration of this NCD, CMS should explicitly state its role in defining the research questions, study design, and methodological approach for CMS-approved clinical research. Based on the revised CED guidance, CMS' role remains unclear. For example, the reconsideration of the NCD notice raises the possibility that CMS may establish criteria for Medicare beneficiaries to be included in the research. We recommend that CMS maintain flexibility when developing such criteria, defining a process to work with study sponsors and principal investigators to address the inclusion of Medicare beneficiaries in CMS-approved research. Finally, we support CMS' intention to define clearly the role of Federal agencies in overseeing IND exempt trials. In this regard, CMS should define Medicare payment rules for IND exempt trials. The independent authority of FDA should be maintained and the FDA should continue to regulate IND exempt trials.

Conclusion

Pfizer appreciates the opportunity to provide CMS with specific recommendations on the reconsideration of the clinical research policy. We would welcome an opportunity to meet with

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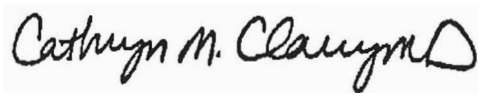
[6] Centers for Medicare & Medicaid Services. Draft Guidance for the Public, Industry and CMS Staff: National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development. Available at: https://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8. Issued July 12, 2006.

[7] Centers for Medicare & Medicaid Services. Criteria for Review of Requests for CMS Research Identifiable Data (Criteria #7). Available at http://www.cms.hhs.gov/PrivProtectedData/02_Criteria.asp. Accessed August 2, 2006.

[8] National Institutes of Health. Final NIH Statement in Sharing Research Data. Notice #NOT-OD-03-032. Available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html. Issued February 26, 2003.

the Agency during the development of this NCD. Please feel free to contact me directly at 212-733-6973 with any questions, or if you need additional information on our above comments.

Sincerely,



Cathryn M. Clary, MD

cc: Barry Straube, M.D., Chief Medical Officer, and Director, Office of Clinical Standards and Quality, CMS
Steve Phurrough, MD, MPA, Director, Coverage and Analysis Group, CMS

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Sent electronically to: CAGInquiries@cms.hhs.gov

Re: **Reconsideration of the Clinical Trial Policy (CAG-00071R)**

Dear Drs. Phurrough and Fitterman:

The National Patient Advocate Foundation (NPAF) is a non-profit organization dedicated to improving access to health care services through policy reform. The advocacy activities of NPAF are informed and influenced by the experience of patients who receive counseling and case management services from our companion organization, the Patient Advocate Foundation (PAF), which specializes in mediation for access to care, job retention, and relief from debt crisis resulting from diagnosis with a chronic, debilitating or life-threatening disease. In 2005, PAF was contacted by 4.1 million patients requesting information and/or direct professional intervention in the resolution of access disputes. In 2005, 102,500 patients contacted PAF seeking enrollment into clinical trials as reported in the Patient Data Analysis Report of 2005 for PAF. Of that number, 28,187 patients were enrolled as Medicare Beneficiaries. As a non-profit involved for many years in the work to gain coverage of clinical trials through the Patient Bill of Rights, we supported the Executive Memorandum of 2000 to lend this support.

We are writing in response to the Centers for Medicare and Medicaid Services' (CMS) reconsideration of its Clinical Trial Policy (to be renamed the Clinical Research Policy), which it originally developed through the national coverage determination process (hereinafter referred to as the "NCD"). NPAF applauds CMS for recognizing that several issues have surfaced since the implementation of the current policy on September 19, 2000 that are creating obstacles to improving Medicare beneficiary enrollment in clinical trials. At the same time, NPAF urges that no revisions compromise or diminish the current level of coverage available to beneficiaries.

The Clinical Trial Policy was developed in response to an Executive Memorandum issued by President Bill Clinton. The July 7, 2000 Executive Memorandum noted:

> [U]ncertainty regarding reimbursement often deters patients from participating in these trials, and deters physicians and other clinicians from recruiting patients, contributing to

low participation rates and slowing the development of new medical treatments and diagnostic tests that could benefit the entire Medicare population.[1]

Unfortunately, the goal of the Executive Order – to increase Medicare beneficiary participation in clinical trials - remains to be achieved because the coverage offered by the policy applies only to a small portion of clinical trials and because the Clinical Trial Policy is imbued with ambiguities. In fact, a study published earlier this year found that although "older patient representation in clinical trials has increased in recent years, it remains well below the expected rate."[2] The authors concluded that in order to reach this goal there needs to be improvement in the Medicare payment structure, among other things.[3]

NPAF offers the following recommendations to help CMS develop a new Clinical Research Policy that successfully promotes greater access to clinical research studies.

1. Adopt a definition of "Therapeutic Intent" that is not tied to trial phase

In order for an item or service furnished as part of a clinical trial to be covered by Medicare, the trial must be a "qualified" clinical trial. To be qualified, the trial must, among other things, have therapeutic intent. Yet, except for a parenthetical remark that states a trial should not be designed exclusively to test toxicity or disease pathophysiology, the NCD offers no guidance as to how the presence or absence of therapeutic intent should be determined. Consequently, there has been considerable confusion among health care providers and suppliers as to what factors to consider dispositive of therapeutic intent. CMS itself has acknowledged that the term is "open to interpretation."[4]

NPAF urges CMS to adopt a broad definition for therapeutic intent that recognizes that therapeutic intent can be demonstrated through a variety of indicia, including measurement of patient outcomes (e.g., survival and quality of life measures) or laboratory markers (e.g., tumor size alterations). The presence of therapeutic intent also is discernable from the expectations of the investigator and the patient enrolled in a trial. When a physician seeks to enroll a patient with cancer in a trial testing a new drug or a new combination of approved drugs it is without doubt that both patient and doctor are hopeful that the therapy will improve the patient's outcome. It would be unethical for a physician to steer a patient toward an investigational therapy, if there is a known treatment for what ails the patient.

CMS should not rely on mechanistic indicia such as the phase of a trial or whether treatment of disease or injury is listed a primary or secondary objective of a protocol. NPAF believes either approach would be to inject form over substance as both utterly fail to recognize that for individuals suffering from life threatening diseases like cancer, a clinical trial (regardless of its designated Phase) is usually a beneficiary's only remaining opportunity to impact the course of their disease. The NCD should not cut off access to what may be a final lifeline by denying coverage for routine items and services furnished under a protocol that would be categorized as a Phase I or Phase II trial.

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[1] Memorandum on Increasing Participation of Medicare Beneficiaries in Clinical Trials, 36 *Weekly Cop. Pres. Doc.* 1311, 1312 (June 7, 2000).

[2] Joseph M. Unger *et al.*, *Impact of the Year 2000 Medicare Policy Change on Older Patient Enrollment to Cancer Clinical Trials*, 24 J. Clin. Oncol. 141, 141 (January 1, 2006).

[3] Id at page 141.

[4] *CMS Response to Questions About Medicare Reimbursement of Clinical Trial Costs*, 5 Medical Research Law & Policy 264 (April 5, 2006) (reprinted from the "Members Only" section of the American Health Lawyers Association website).

2. Develop a qualifying process for non-deemed trials

Medicare reimburses routine costs only for "qualified" clinical trials. When the NCD originally was drafted in 2000, CMS envisioned two qualification processes for clinical trials. First, some clinical trials (e.g., trials funded by Federal agencies such as the National Institutes of Health) are deemed to be qualified. Second, sponsors were to self-certify that other trials (e.g., trials funded by private industry and academic institutions) meet qualifying criteria developed by the Agency for Healthcare Research and Quality (AHRQ) and other Federal agencies. Although a multi-agency taskforce developed and forwarded criteria to CMS, the criteria have not yet been finalized.[5] CMS now proposes to remove the self-certification option.[6]

NPAF urges CMS to develop a qualifying process for non-deemed trials. Statistics show that about half of all clinical trials are sponsored by private industry or academic institutions[7] and, thus, are not automatically deemed to be qualifying trials. Consequently, Medicare beneficiaries face reimbursement barriers for about half of all clinical trials.

NPAF thinks that CMS should adopt a process that would qualify any scientifically sound clinical trial, regardless of whether the Federal government or private industry or academia sponsors the study. The process should be clear and easily implemented by sponsors. CMS should not delegate responsibility for determining "qualified" clinical trials to the carrier or fiscal intermediary medical directors. Such a delegation will place an enormous administrative burden on these medical directors, and unless the carriers and fiscal intermediaries have additional resources to handle these complicated reviews access to trials will be unduly delayed. Moreover, the medical directors may not have the expertise to judge the merits of a protocol (e.g., a CMD who is a psychiatrist may not be adequately qualified to assess the merits of an oncology study). Finally, medical directors may reach different conclusions regarding the qualification of a particular study. This could lead to geographic differences in coverage which is inconsistent with the national purpose of the NCD. And if a carrier medical director and fiscal intermediary medical director in the same jurisdiction disagree on coverage for a particular trial, a beneficiary might be in a situation where the routine physician services under a protocol might be covered but the hospital services are not (or vice versa). Such a perverse result is not acceptable.

3. Allow sponsors to cover costs not reimbursed by Medicare

Clinical trial agreements often contain language ensuring that the sponsor will cover certain costs if not reimbursed by another payor (e.g., cost for trial-related injuries). CMS has interpreted such statements to mean that the trial sponsor is accepting responsibility as the primary payor of all clinical trial services and that Medicare is the secondary payor.[8] CMS's application of the Secondary Payor Rule to clinical trial agreements is flawed and impedes beneficiary enrollment in trials and places those in trials at unnecessary financial risk.

The Medicare statute precludes payment when "payment has been made or can reasonably be expected to be made under a liability insurance policy or plan". Agreements by sponsors to pay for items or services for which Medicare or another third-party payer refuses payment serve only as a promise to pay for services that

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[5] Mark Barnes and Jerald Korn, *Medicare Reimbursement for Clinical Trial Services: Understanding Medicare Coverage in Establishing a Clinical Trial Budget*, 38 J. Health L. 609, 623 (2005).

[6] Issue 5 in the NCA Tracking Sheet for Clinical Trial Policy (CAG-00071R).

[7] Carol Rados, *Inside Clinical Trials: Testing Medical Products in People*, 37 FDA Consumer Magazine (September – October 2003) (*available at* http://www.fda.gov/fdac/features/2003/503_trial.html). Rados reported that in 2003, there were 5413 sponsored clinical trials (2781 sponsored by NIH; 186 sponsored by other Federal agencies; 668 sponsored by industry; and 1778 sponsored by academic institutions).

[8] Letter from Gerald Walters, Director, Office of Financial Services Group, Office of Financial Management, to Holley Thames Lutz, Esq., Gardner, Carton & Douglas, LLP (April 13, 2004).

are otherwise not covered by a payer. Thus, payment from a sponsor for items or services for which Medicare or another third-part payer is supposed to cover "cannot reasonably be expected." If the coverage and payment policies of third-party payors, including Medicare, were more transparent and consistently applied then sponsors would have the ability to provide beneficiaries with an itemized list of the costs it would cover, but this is not case. We know, based on the work of PAF, that every year thousands of patients are financially devastated by bills for health care services they believed would be covered by their insurer. Sponsors are trying to provide beneficiaries with some assurance that this will not happen to them. Yet, Medicare's interpretation of its secondary payer rules is leaving sponsors with no choice but to discontinue offering assistance to beneficiaries. Consequently, patients are left at risk and are unwilling to enroll in trials.

We urge CMS to revisit its interpretation of the secondary payer rules, and if necessary, make regulatory changes that would allow sponsors to cover all costs not reimbursed by another payor.

4. CMS should use caution in adopting criteria mandating enrollment of a representative sample of Medicare beneficiaries

CMS has proposed development of "criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries, by demographic and clinical characteristics."[9] While NPAF recognizes the importance of understanding the impact of new treatments across many subpopulations, we believe CMS must provide a marketing process that informs seniors of their clinical trials coverage options. Outreach to non-profits, national advertising campaigns and community outreach would constitute minimum outreach required. Web interaction would also be recommended as secondary support to the process. With outreach, CMS must engage providers actively in recruitment drives to assure the minimum requirements are met. Absent this collaborative approach, NPAF would encourage that no minimum be required.

With outreach and collaborative plans to enroll seniors, NPAF would caution that the research community must define minimum enrollees based on their experiences in treating the nation's seniors. CMS is further cautioned to administratively define a minimum absent direction from oncology clinicians and researchers involved daily in efforts to enroll seniors. The burden of fulfilling such a mandate could unnecessarily prolong the length of a clinical trial and slow access of the Medicare population as whole to what might be an important new treatment. Moreover, it would unfairly exclude patients just because they do not happen to be Medicare beneficiaries. NPAF believes that it is more appropriate to use the Coverage with Evidence Development mechanism to gather specifics about the efficacy of a treatment in the elderly rather than mandate their inclusion in clinical trials.

5. CMS should expand coverage to include studies and items or services that traditionally have been excluded

We commend CMS for taking steps to expand Medicare coverage to include research studies other than clinical trials as well as items or services that traditionally have been excluded from coverage.

NPAF agrees with CMS that Medicare's routine cost reimbursement should apply in the context of non-traditional clinical research studies (e.g., trials and registries created for Coverage with Evidence Development, studies that are not randomized, studies involving observational registries). NPAF also agrees with CMS that "items/services that do not meet the requirement of 1862(a)(1)(A) but are of potential benefit"

[9] Issue 3 in the NCA Tracking Sheet.

should be covered.[10] Similarly, NPAF urges CMS to adopt payment criteria for items or services, otherwise not covered but are used "in the context of clinical research to elucidate the impact of the item or service on health outcomes in Medicare beneficiaries."[11]

By expanding the universe of covered clinical research studies as well as items and services, CMS will allow beneficiaries to access a greater set of innovative therapies.

* * *

NPAF appreciates this opportunity to comment on CMS' reconsideration of its Clinical Trial Policy (to be renamed the Clinical Research Policy). We look forward to a maintaining a policy that will improve Medicare beneficiaries' access to clinical research. We would be available to share more detailed information with CMS regarding the difficulties of increasing clinical trial enrollment. Please do not hesitate to call me at (202) 347-8009.

Respectfully submitted,

Nancy Davenport-Ennis

Nancy Davenport-Ennis
Chief Executive Officer

[10] Issue 8 in the NCA Tracking Sheet. Section 1862(a)(1)(A) of the Social Security Act states that Medicare will make no payment for items and services that are "not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."
[11] Issue 9 in the NCA Tracking Sheet.

ONS
Where Oncology Nurses Connect

Oncology Nursing Society

125 Enterprise Drive • Pittsburgh, PA 15275-1214
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August 2, 2006

The Honorable Mark B. McClellan, M.D., Ph.D.
Administrator
Centers for Medicare and Medicaid Services
U.S. Department of Health and Human Services
Room 445-G
Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20001

Dear Administrator McClellan:

On behalf of the Oncology Nursing Society (ONS) - the largest professional oncology group in the United States, composed of more than 33,000 nurses and other health professionals dedicated to ensuring access to quality care for people with cancer - we are writing to comment on the Centers for Medicare and Medicaid Services' (CMS) policy regarding coverage for the patient care costs associated with participation in clinical trials. ONS has a long-standing position that asserts "participation in clinical trials must be a standard benefit of all [public and private] health insurance plans and legislation must be adopted to prohibit denials of trial-associated patient care reimbursement costs."* As such, ONS generally supports the National Coverage Decision that implemented the 2000 Executive Memorandum which directed Medicare to pay for routine patient care costs associated with participation in clinical trials.

The goal of ONS and the other cancer community stakeholders who sought the 2000 Executive Memorandum was to boost significantly the number of Medicare beneficiaries with cancer who participate in clinical trials in order for them to receive care that may have a health benefit and to encourage the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies in the Medicare population, thus improving the quality of care that Medicare beneficiaries receive. It is our understanding that since the issuance of the National Coverage Decision, the percentage of Medicare beneficiaries with cancer participating in clinical trials has increased approximately 13%. While this increase is not insignificant, ONS has concerns that not all Medicare beneficiaries have adequate access to clinical trials. ONS works hard to educate its members about ways in which barriers to clinical trials can be eliminated. It has been brought to our attention that many Medicare beneficiaries who are enrolled in Medicare managed care plans and those in fee-for-service Medicare who are without a supplemental coverage have lower rates of participation in clinical trials than those beneficiaries in traditional fee-for-service Medicare and who have a supplemental coverage policy. We urge CMS to explore this

* To view the entire ONS position statement on "Cancer Research and Cancer Clinical Trials," visit: http://www.ons.org/publications/positions/CancerResearch.shtml.

disparity and to take action to ensure that all Medicare beneficiaries with cancer who wish to enroll in a clinical trial can do so without economic hardship or the imposition of alternate billing conditions to those under which they receive their other care.

While some modifications to the National Coverage Decision may be necessary to address implementation issues, we maintain that the current policy is having its intended impact - increasing the number of Medicare beneficiaries with cancer who participate in clinical trials. ONS supports a review of the current policy but maintains that any changes that narrow or otherwise limit the coverage policy would have serious adverse effects on Medicare beneficiary participation in clinical trials. Therefore, as you review the current policy, we urge you to only make changes that would enhance and expand beneficiary participation in clinical trials.

Thank you again for your attention to our concerns. We look forward to working with you and your colleagues to ensure that all Medicare beneficiaries with cancer have access to - and coverage of - cancer care provided in the context of clinical trials. Please do not hesitate to contact us or our Washington, DC Health Policy Associate Ilisa Halpern Paul (202-230-5415, ipaul@gcd.com) should you have any questions about these or other cancer or nursing-related issues.

Sincerely,

Georgia M. Decker, MS, RN, CS-ANP, AOCN®
President

Pearl Moore, RN, MN, FAAN
Chief Executive Officer

3-1-06

Cancer Research and Cancer Clinical Trials

"The costs, both human and economic, of cancer in this country are catastrophic. Our national investment in cancer research is the key to bringing down spiraling healthcare costs and to supporting a thriving economy" (National Coalition for Cancer Research, 2001). Since the 1971 signing of the National Cancer Act that established the "War on Cancer," there have been innumerable fundamental discoveries about how cancer develops and progresses. These findings provide the blueprint for completely new therapies that exploit the characteristic molecular abnormalities of cancer cells. Financ support for all facets of cancer research, including cancer clinical trials (cancer resear studies with patients), is essential to prevent, effectively treat, and manage the short- and long-term sequelae of cancer, as well as all critical elements of quality cancer car

It Is the Position of ONS That

- Federal funding for all levels of cancer research must be significantly increased
- All clinical trials must be peer reviewed, include participant informed consent, a be approved through an institutional review board process.
- Every person diagnosed with cancer must have the right to participate in a clini trial if medically indicated.
- Individuals at high risk for cancer or those who wish to change behaviors that increase cancer risk must be offered the opportunity to participate in cancer prevention trials. The goal of these trials is to reduce cancer incidence and mortality.
- All barriers to participation in clinical trials, including both recruitment and retention, must be abolished.
- Participation in clinical trials must be a standard benefit of all health insurance plans, and legislation must be adopted to prohibit denials of trial-associated patient care reimbursement costs.
- Content related to cancer research and clinical trials must be incorporated into basic educational curricula of healthcare professionals and fostered through continuing education.
- More effective strategies to promote public awareness and understanding of cancer research and clinical trials must be devised, implemented, and evaluate
- Improved strategies to facilitate the participation of underrepresented populatio must be devised, implemented, and evaluated.
- Concepts of quality cancer care, as defined by ONS in its position on "Quality Cancer Care," must be incorporated into the planning and coordination of clinic trials.
- Coordination of clinical trials (e.g., coordination of clinical sites, development of standardized treatment orders, symptom management, patient education and advocacy, facilitation of informed consent, assistance with participant accrual a retention) is best accomplished by RNs who have been educated and certified i oncology nursing.
- Nurses design, initiate, and facilitate clinical research studies to address quality of-life issues for people with cancer. The goal of quality-of-life research is to improve the lives of those who have been affected by cancer.
- Continuing informed consent must be ensured for all individuals considering or

participating in clinical trials.
- Solutions or innovative strategies to decrease financial burdens associated with institutional participation in clinical trials must be devised.

Background

The spectrum of cancer research includes basic science that promotes the understanding of the molecular and genetic bases of cancer, as well as the translatior this knowledge to practice for prevention, early detection, and disease management. Clinical trials facilitate discovery and implementation of preventive and early-detection strategies, provide the best available treatment and symptom management, and explc and define rehabilitation and survivorship needs to enhance quality of life for those wh face the challenges imposed by cancer. Oncology nurses have a critical role in the conduct of both cancer treatment and prevention trials (Aikin, 2002; Klimaszewski et a 2000).

Only 3% of U.S. cancer healthcare costs currently are invested in cancer research (National Coalition for Cancer Research, 2001). Fewer than 3% of adults with cancer participate in clinical trials, despite estimates that 12%–44% of adults with cancer are eligible for entry into these research studies (Morrow, Hickok, & Burish, 1994). In his testimony before the House of Representatives Committee on Government Reform (M 13, 2004), Robert L. Comis, MD, president and chair of the Coalition of National Canc Cooperative Groups, stated the following: "The cooperative groups have been and remain chronically underfunded. Two extensive reviews of the system in the mid-1990 recommended that the cooperative groups be funded at the full peer-review recommended level. We continue to be funded at approximately 60% of that level, anc funding has been flat for the last three years. This stifles innovation, destabilizes key functions such as our tissue banks, data management and informatics platforms, and acts as a disincentive to both academic and community physician participation. . . . Th cooperative groups remain totally committed to providing high-quality care and new opportunities for our cancer patients. But rest assured, the development of the newer cancer treatments will make clinical trails more complicated and more costly."

Barriers to access and enrollment in clinical trials include system barriers, healthcare provider barriers, and patient barriers. Modifying attitudes, changing perceptions, and increasing awareness about clinical trials among these groups are paramount to overcoming many of the present barriers.

The ONS Health Policy Agenda identifies the commitment and responsibility of the Society and its members to advocate for the well-being of people affected by cancer. Advocating for the optimal approach for each person potentially or actually affected by cancer, including the assurance of complete disclosure of treatment options and potential risks and benefits associated with these options and ongoing informed conse to the option to be pursued, is essential to quality cancer care.

Approved by the ONS Board of Directors June 1998; Revised June 2000, July 2002, August 2004.

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Morrow, G., Hickok, J., & Burish, T. (1994). Behavioral aspects of clinical trials. *Cance 74*, 2676-2682.

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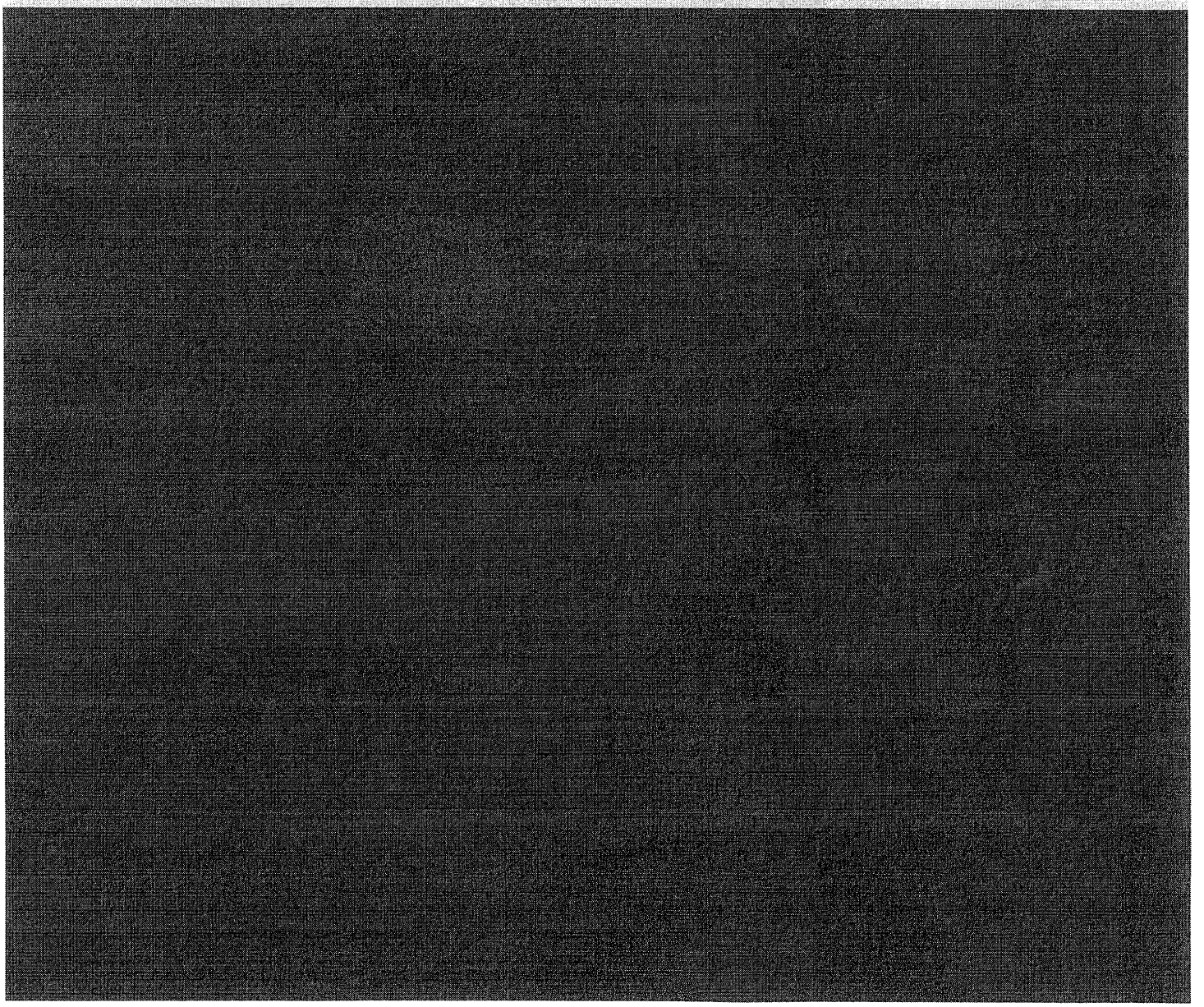
The Board of Directors acknowledges the contributions and expertise of the members the ONS Clinical Trial Nurses Special Interest Group who assisted in the developmen and review of this position.

To obtain copies of this or any ONS position, contact the Customer Service Center at ONS National Office at 125 Enterprise Drive, Pittsburgh, PA 15275-1214 (866-257-4ONS; customer.service@ons.org). Positions also may be downloaded from the ONS Web site (www.ons.org).



JOHNS HOPKINS
MEDICINE
SCHOOL OF MEDICINE

Daniel Ford, M.D., M.P.H.
Vice Dean for Clinical Investigation

August 9, 2006

CLINICAL TRIAL NCD RECONSIDERATION
Proposed Comments

Leslye K. Fitterman, Ph.D.
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Dear Dr. Fitterman:

The Johns Hopkins University and the Johns Hopkins Health System ("Hopkins") welcome this opportunity to set forth their comments to the Centers for Medicare and Medicaid Services ("CMS") as it reconsiders its national coverage decision on the Clinical Trial Policy.

When CMS made its recent announcement of its decision to reconsider that policy, it announced that certain revisions might be necessary to accomplish the following three overarching goals:

1) to allow Medicare beneficiaries to participate in research studies;
2) to encourage the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies in the Medicare population, thus improving the quality of care that Medicare beneficiaries receive; and,
3) to allow Medicare beneficiaries to receive care that may have a health benefit, but for which evidence for the effectiveness of the treatment or service is insufficient to allow for full, unrestricted coverage.

Hopkins believes these goals are the appropriate goals for the development of a revised national coverage decision and they are goals Hopkins fully supports.

CMS identified the following key issues for which it has requested comments. Johns Hopkins' comments are set forth below in response to each issue identified by CMS:

1) **Clarify payment criteria for clinical costs in research studies other than clinical trials;**

Hopkins believes that the payment criteria for any clinical costs in research studies should be based upon the overarching goals identified by CMS: to allow Medicare beneficiaries to participate in research studies, to encourage the conduct of research studies that add to the

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knowledge base regarding products and technologies (and thereby having the long-term benefit of improving quality of care for Medicare beneficiaries), and to allow Medicare beneficiaries to receive care that may have a health benefit. Any clarification should be consistent with these goals.

2) Devise a strategy to ensure that Medicare covered clinical studies are enrolled in the National Institutes of Health (NIH) clinical trials registry website;

Hopkins agrees with CMS's goal of broadening the use of the NIH trials registry and other similar registries.

3) Develop criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries, by demographic and clinical characteristics;

Hopkins believes that study design and patient enrollment must be driven solely by the clinical goals and the criteria related thereto. Therefore, the scientific purpose of the study should determine who is eligible for the study. Any assessment of the final study sample to determine representativeness for all Medicare beneficiaries would be too scientifically and operationally complex to be useful.

4) Clarify the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials;

Hopkins believes that the existing definitions of routine clinical care costs set forth in the September 19, 2000 National Coverage Decision are reasonable and provide the appropriate room for the exercise of medical judgment.

5) Remove the self-certification process that was never implemented;

Hopkins believes that CMS should maintain and further clarify the "deemed" criteria in the NCD as it relates to trials supported by centers or groups that are funded by NIH, CDC, AHRQ, CMS, DOPD and VA. Hopkins believes that CMS should provide further interpretation to confirm that, for example, an NCI-designated Comprehensive Cancer Center or Clinical Cancer Center would meet its definition of a center supported and funded by the NIH.

6) Clarify the scientific and technical roles of Federal agencies in overseeing IND Exempt trials;

Hopkins believes the coverage criteria applied to off-label drug use should also be applied to IND-exempt drugs when used in a research study. The process used by Medicare contractors for determining coverage for an off-label drug involves determining whether the drug is listed in certain national compendia as the standard of care through peer review journals and similar standards. If it is listed, the drug is eligible for Medicare coverage. Applying a similar policy to off-label drugs would be consistent with the language of the original NCD transmittal and the

CMS questions and answers which explain that the policy did not remove coverage already provided under local or national policy.

In addition, IRBs currently provide oversight of compliance with the FDA's IND-exempt criteria that the use of the drug meets the requirements of federal regulations.

7) Determine if coverage of routine clinical care costs is warranted for studies beyond those covered by the current policy.

As noted above in addressing the issue of payment criteria for clinical costs in research studies, Hopkins believes coverage of routine clinical costs should be determined based on whether the research study meets the CMS goal of encouraging the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost–effective use of products and technologies in the Medicare population, or meets the goal of allowing Medicare beneficiaries to receive care that may have a health benefit, but for which evidence for the effectiveness of the treatment or services is insufficient to allow for full, unrestricted coverage.

8) Clarify how items/services that do not meet the requirements of 1862(a)(1)(A) but are of potential benefit can be covered in clinical research studies as an outcome of the National Coverage Determination process;

Hopkins believes that preventive trials should be equally covered to the extent that they meet the CMS goals discussed in our response to the issue addressed immediately above.

9) Clarify whether and under what conditions an item/service non-covered nationally may be covered in the context of clinical research to elucidate the impact of the item or service on health outcomes in Medicare beneficiaries; and

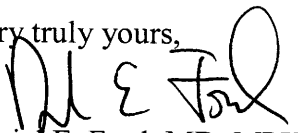
Hopkins believes it is important for CMS to continue to be open to coverage for new treatments and technologies. CMS has historically approved coverage for particular new technologies conditioned upon clinical studies to evaluate efficacy and cost effectiveness, and this approach should be continued.

10) Discuss Medicare policy for payment of humanitarian use device (HUD) costs.

Hopkins is supportive of CMS's current policy to pay for humanitarian use devices.

Hopkins appreciates the opportunity to make these comments.

Very truly yours,



Daniel E. Ford, MD, MPH
Vice Dean for Clinical Investigation
Johns Hopkins School of Medicine

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

July 27, 2004

The Honorable Mark A. McClellan, MD, PhD
Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
7500 Security Boulevard
Room C5-25-25
Baltimore, MD 21244-1850

Dear Dr. McClellan:

The American Society of Clinical Oncology (ASCO) would like to bring to your attention a Medicare policy that adversely affects cancer patients enrolled in Medicare Advantage plans. ASCO is the national organization representing physicians who specialize in the treatment of cancer, and we are concerned about how this policy is harming our patients. Moreover, the policy does not appear to be consistent with legal requirements. We would appreciate your review of the matter.

On September 19, 2000, CMS published a national coverage determination (NCD) extending Medicare coverage to certain services furnished as part of designated clinical trials. Section 1852(a)(5) of the Social Security Act provides that an NCD that will result in a significant change in costs does not apply to a Medicare Advantage (or, formerly, Medicare+Choice) organization until the contract year after the next announcement of capitation rates. As a result, the NCD on clinical trials did not apply to Medicare managed care plans until 2002, and in the interim, CMS directly paid providers that furnished clinical trial services to Medicare+Choice enrollees on a fee-for-service basis.

Section 1853(c)(7) of the Act provides that CMS "shall adjust appropriately the payments to [Medicare Advantage] organizations" beginning with the first contract year after the announcement of capitation rates following issuance of an NCD. CMS, however, did not adjust the capitation rates for 2002 to reflect any additional costs due to the NCD on clinical trials. Instead, section 55 (chapter 7) of the Medicare Managed Care Manual states that CMS determined that the capitation rates for 2002 "do not reflect any adjustment for this significant cost NCD" and therefore continued the policy of paying providers directly for clinical trial services furnished to Medicare managed care plan enrollees. This policy continues to be in effect.

Since CMS is paying for clinical trial services on a fee-for-service basis, beneficiaries are ordinarily responsible for the coinsurance payments associated with fee-for-service payments, e.g., 20 percent in the case of physician services, including drugs furnished incident to physicians' services. For the period beginning in 2002, CMS advised Medicare+Choice organizations that they could alter this coinsurance structure within the normal rules applicable to Medicare+Choice plans, but they were not required to do so.

As a result of CMS's policy, many Medicare Advantage enrollees with cancer are effectively denied the access to clinical trials that is afforded to beneficiaries in the traditional Medicare program. Medicare Advantage enrollees frequently cannot afford the high coinsurance associated with fee-for-service Medicare, and, because they are enrolled in Medicare Advantage plans, they do not have the supplemental insurance that beneficiaries enrolled in the traditional Medicare program typically have. Consequently, physicians who would otherwise enroll their Medicare Advantage patients in clinical trials are not doing so.

We do not understand how CMS's policy is consistent with the requirement in section 1853(c)(7) that the capitation payments be adjusted to reflect any significantly increased costs of an NCD. Instead of adjusting the payments, CMS appears to take the position in the Managed Care Manual, as quoted above, that the agency is required to determine whether the capitation rates have adjusted themselves and is permitted to pay providers outside the capitation rate system if they have not.

The managed care industry has raised concerns about including the costs of clinical trials in the capitation rates, as indicated by the following Q&A on the CMS website:

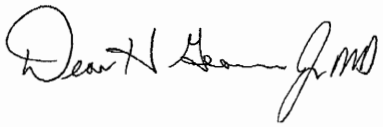
> "Q5. M+C organizations are very concerned about how they are going to cover these costs once they are included in capitation payments. How are M+C organizations' questions going to be resolved?
>
> "A5. M+C organizations and their representatives have raised many important questions about how this will work, and HCFA will continue ongoing discussions with industry representatives to resolve operational issues. HCFA will be developing answers to questions of this nature that were submitted as part of the comment process for the NCD and publishing them on an ongoing basis on the hcfa.gov web site."

We did not locate any information on the CMS website indicating resolution of the issues alluded to in this Q&A. In any event, these concerns do not appear to be a sufficient basis to avoid the statutory requirement to adjust the capitation rates to account for new NCDs.

Clinical trials often represent the best possible treatment for cancer patients as well as an important opportunity to demonstrate the comparative effectiveness of various therapies. We urge CMS to remove the current obstacle to Medicare Advantage enrollees participating in clinical trials by promptly incorporating any additional costs into the capitation rates so that the plans must cover clinical trial services on the same basis as other services.

Thank you for your attention to this issue.

Sincerely,



Dean Gesme, Jr., MD
Chair, Clinical Practice Committee

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, Maryland 21244-1850

CMS
CENTERS for MEDICARE & MEDICAID SERVICES

CENTER FOR BENEFICIARY CHOICES

SEP 2 2 2004

Dr. Dean Gesme, Jr.
Chair, Clinical Practice Committee
American Society of Clinical Oncology
1900 Duke St., Suite 200
Alexandria, VA 22314

Dear Dr. Gesme:

Your letter to the CMS Administrator, Dr. Mark A. McClellan, concerning Medicare Advantage (MA) patients enrolled in clinical trials was referred to me for a reply. You asked about CMS policy on coverage of certain benefits related to clinical trials as a result of the National Coverage Determination (NCD) published on September 19, 2000. In accordance with section 1853(c)(7) of the Social Security act, because the cost of covering these new benefits has not yet been included in the MA capitated payment rates, and since this cost met the threshold requirement in regulations at 42 CFR 422.109, CMS has determined that providers continue to be paid directly for covered clinical trial services furnished to Medicare managed care plan enrollees.

Your concern is with respect to CMS policy that MA plan enrollees are responsible for any cost-sharing amounts imposed under original Medicare rules for these services, or any other cost-sharing structures for these services plans may choose to impose and approved by CMS. You stated that this policy makes covered clinical trial services unaffordable for many MA plan enrollees. You also expressed some concern that CMS has not yet adequately adjusted MA plan rates to account for the costs of covered clinical trial services.

First, we don't agree that MA plan enrollees are unfairly disadvantaged by this policy. Under the policy described for cost-sharing liability, both original Medicare beneficiaries and MA plan beneficiaries will in effect be responsible for the same level of cost-sharing for covered clinical trial services. MA plan materials should include notification of such cost-sharing liability prior to the time a Medicare beneficiary chooses to enroll in a clinical trial.

Second, at this time CMS has not adjusted MA plan rates to account for the costs of clinical trials so payment continues to be made on a fee-for-service basis directly to the providers of services. We review MA rates each year and will continue to consider the costs of clinical trials. You may want to submit comments regarding payment for clinical trial services in response to the Advance Notice of Methodological Changes for 2005 MA payment rates in spring 2005 .

I agree that clinical trials are often the best possible treatment for some patients and we would certainly encourage all beneficiaries to be informed of the treatment possibilities posed by clinical trials.

Sincerely,

Tom Hutchinson
Director
Medicare Plan Policy Group

Larry J. Goodman, MD
President
Chief Executive Officer

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RUSH UNIVERSITY
COLLEGE OF NURSING
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August 9, 2006

Leslye K. Fitterman, Ph.D.
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244-1849

Re: Medicare Clinical Trial Policy

Dear Dr. Fitterman:

I write today on behalf of Rush University Medical Center to provide comments on the Centers for Medicare & Medicaid Services' ("CMS") public notice of its reconsideration of the National Coverage Decision on Routine Costs in Clinical Trials (the "Clinical Trials NCD"), to be renamed by CMS, the "Clinical Research Policy."

As a preliminary matter, I applaud CMS's willingness to revise the Clinical Trials NCD. As you know, Rush voluntary disclosed overpayments it received related to cancer clinical trials and reached a settlement with the federal government in December 2005. The matter was initially discovered and self-disclosed in the summer of 2003. Over the past three years Rush has diligently set out to devise operational processes that comply with the Clinical Trials NCD. One of the greatest challenges at the beginning of the process was grappling with the words of the Clinical Trials NCD, many of which are ambiguous and internally inconsistent. The meeting we held with your office in October 2005, and subsequent meetings by Rush representatives with our local Medicare contractor's medical director, were critically important in obtaining clarification and understanding of the Medicare Program's expectations.

Our comments below are born of our experiences as an academic medical center with a trifold mission of health care, education and research. While there is a host of issues that can be raised related to clinical trials billing compliance, we have chosen to focus on the five items below as priority.

The comments below are provided in the context of the assumption that the revised Clinical Research Policy will maintain the concept (though the terms may change) that the Medicare Program will cover "routine costs" of certain "qualifying clinical trials." From a practical perspective, CMS's reconsideration efforts should focus on what constitutes a "routine cost" during a clinical trial and what constitutes a "qualifying clinical trial."

We offer the following comments for your consideration:

1. Coverage Under the Revised Clinical Research Policy Should Focus on the Needs of the Medicare Beneficiary.

The reconsideration Tracking Sheet identifies the following issue for consideration in a new Clinical Research Policy: "Clarify the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials."

One of the clarifications that has been the most helpful in Rush's endeavors to develop clinical trial billing compliance structures was confirming with CMS that generally whatever is covered by Medicare outside a clinical trial is covered during a clinical trial. This assumes of course that the item or service covered is not being paid for by the sponsor or promised free in the informed consent.

Since what is covered outside a clinical trial is dependent upon the patient's needs and whether the item or service is "reasonable and necessary" for the patient, the revised Clinical Research Policy should promote coverage for any item or service during a clinical trial that serves the clinical needs of the patient, providing the service is not paid for by the sponsor or promised free in the informed consent.

While we recognize that Medicare is primarily a public health insurance program, the criteria for Medicare coverage in general laudably focuses on the individual medical needs of the Medicare beneficiary that are "reasonable and necessary for the diagnosis or treatment of illness or injury." (Section 1862(a)(1)(A) of the Social Security Act). The revised Clinical Research Policy should likewise be beneficiary-focused. In defining routine costs, the revised Clinical Research Policy should move away from amorphous terms such as "conventional care" which imply objective standards that do not contemplate the individual needs of a patient enrolled in a clinical trial. CMS should define a "routine cost" of a qualifying clinical trial as *"an item or service that is reasonable and necessary to diagnose or treat a Medicare beneficiary enrolled in a clinical trial, except when the sponsor has agreed to pay for the item or service or when the item or service is offered without charge to the Medicare beneficiary or to the beneficiary's third-party payor."*

Simplifying the definition of a routine cost to focus on medically necessary services for the enrolled patient allows health care providers to stay focused on treating the patient's needs and yet still accomplish the goal of the Medicare Program to cover the same services a patient would receive outside a clinical trial as inside the trial.

This simplified definition also addresses three important matters: a) it obviates the need to define in detail what is not a "routine cost;" b) there is no need to define the details of what is an "investigational cost" (how the investigational item or service can be handled is discussed in the next comment); and c) it also accommodates items and services that are provided to detect, prevent or treat complications.

With respect to this last point, services to detect or prevent complications should be considered as meeting medical necessity criteria based on the potential toxicity of investigational agents or to preserve patient safety from potential adverse events of the investigational items and services. Services to treat complications are by their nature medically necessary. To ensure that there is no confusion over this matter, we suggest that the revised Clinical Research Policy reinforce this with the following clarification: *"This definition of routine cost includes items and services that are reasonable and necessary to detect or prevent complications that are related to the clinical research, including those items and services that may be used by the investigator to determine whether to alter treatment plans to prevent complications."*

The proposed definition of "routine cost" also contemplates items and services that are conducted at the start of a clinical trial for baseline purposes but also may be used to determine whether the patient meets the study's specific inclusion or exclusion criteria. Before beginning most significant treatments, patients outside of a trial received certain tests to determine the treatment plan or whether the treatment should be given at all. The revised Clinical Research Policy should clarify that in a clinical trial as long as the baseline item or service is being provided for medically necessary reasons, then the item or service should be covered if it is reasonable and necessary care (including to determine whether the investigational item or service poses potential complications to the patient that could lead to the patient not participating in the trial or the physician not enrolling the patient). Baseline services also serve to provide data as to whether the patient meets inclusion or exclusion criteria for the research study, but as long as one purpose of the service is reasonable and necessary for the care of the patient, then the fact that the service is also being used for inclusion and exclusion purposes should not prevent Medicare coverage.

Anchoring "routine cost" in medical necessity accomplishes virtually all of CMS's goals for the revised Clinical Research Policy and reduces the need for a complex definition of "routine cost."

2. <u>The Medicare Program Should Cover the Investigational Item or Service if the Investigational Item or Service is Provided for the Medicare Beneficiary's Diagnosis or Treatment.</u>

The current Clinical Trials NCD attempts to exclude from coverage the investigational item or service but then in a confusing manner allows coverage for the investigational item if the local Medicare contractor has issued a policy or determination allowing coverage of the investigational item or service generally. The definition of "routine cost" that we recommend above eliminates the need to treat the investigational item or service differently from other study-required items and service.

The definition of "routine cost" we advance above ensures the integrity of Medicare coverage because an investigational item or service would not be covered by Medicare if it is: paid for by the sponsor; promised free to the Medicare beneficiary or the beneficiary's third-party

payor; is not medically necessary for the diagnosis or treatment of the Medicare beneficiary; or legal authority has excluded its coverage generally.

Additionally, we encourage the Clinical Research Policy to comment on research studies that investigate the off-label combination of commercially approved drugs. As the investigational items of a clinical trial, these off-label use combinations should be covered the same during a clinical trial as they may be covered outside a clinical trial, according to applicable Medicare rules. We urge clarification of the application of coverage rules to off-label use combinations during clinical research.

3. Any Item or Service Required by a Clinical Trial That is Sponsored or Supported by the Federal Government Should be Considered a Covered Item or Service.

The reconsideration Tracking Sheet identifies the following issue for consideration in a new Clinical Research Policy: "Clarify whether and under what conditions an item/service non-covered nationally may be covered in the context of clinical research to elucidate the impact of the item or service on health outcomes in Medicare beneficiaries."

The revised Clinical Research Policy should provide coverage for any item or service required by a trial that is funded or supported by Federal funds and which is not being paid for by the grant or compensation arrangement. This would include clinical research directly funded by the Federal government or supported by the Federal government through cooperative groups.

It has been our experience that Federal agencies and cooperative groups do not contemplate Medicare reimbursement when designing a clinical research study. Foremost in their minds is the science that will help improve medical care. Corresponding grants and cooperative group contracts also do not usually take into consideration Medicare reimbursement rules. There are often many items and services that are not covered by Medicare in these Federally-supported trials. Providers who accept the Federally-supported trials have almost no ability to negotiate compensation for these trials. Meanwhile, the studies may require a variety of items and services that go beyond conventional care and may or may not be performed to detect or prevent complications. The choice a provider has in these instances is to either pass along these extraordinary costs to the Medicare beneficiary or to subsidize these non-covered costs itself.

A typical example of such a situation is a cooperative group study that investigates the off-label combination of two chemotherapeutic drugs. Because off-label use of drugs involves commercially approved drugs, the cooperative group studies rarely provide supplies of these drugs. In many instances the drugs may not be covered by Medicare because the off-label use has not been medically accepted in drug compendia, in medical literature, or subject to a Local Coverage Determination. Indeed, the lack of data on the efficacy of a promising off-label combination is the very reason why the Federal government or the cooperative group has made the clinical research worthy of Federal support. With no coverage for these expensive drugs, a provider is caught between either subsidizing the cost of the drugs itself or charging the patient for these non-covered items. The revised Clinical Research Policy

should provide coverage for study services that are required by a Federally-supported clinical trial protocol but for which the grant does not afford reimbursement or compensation or supplies of the investigational agent.

4. Achieving Representative Samples of Medicare Beneficiaries in Clinical Trials.

The reconsideration Tracking Sheet identifies the following issue for consideration in a new Clinical Research Policy: "Develop criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries, by demographic and clinical characteristics."

While we heartily encourage the Federal government to support increased medical research for Medicare beneficiaries and develop innovative ways to provide greater access to clinical trials to Medicare beneficiaries, we believe requiring clinical trials to have any type of critical mass of Medicare beneficiaries before a clinical trial qualifies for coverage will produce the opposite effect that CMS seeks.

At the time a research study is developed and approved for enrollment, it is not known when the study will enroll any particular number of Medicare beneficiaries. Trials may be open for enrollment for several years. Any criteria that require certain numbers of Medicare beneficiary enrollees could leave claims and costs for study-related services in limbo for years. Any such criteria would also make negotiating sponsorship agreements fraught with difficulty.

5. Coverage for a Clinical Trial Should be Consistent Throughout the United States.

While we recognize that the coverage authority of Local Coverage Determinations (LCDs) is part of the structure of the Medicare Program designed by Congress and is beyond the control of CMS and beyond the scope of the reconsideration notice (see definition of Local Coverage Determination in Section 1869(f)((2)(B) of the Social Security Act), we wish to call attention to the confusion sewn by LCDs that may differ by region as well as varying approaches to clinical trial coverage by different local Medicare medical directors.

Certain aspects of the Medicare Program were designed for a different era. The regional deference afforded to local Medicare contractors does not make sense in the context of clinical research in which all enrollees of a specific study generally must receive the same services for the same reasons. Differing views of the same clinical trial by Medicare contractors is wholly unnecessary when a particular trial is the same throughout the United States. The variations in the application of coverage rules to clinical trial services defeats the goal of placing trials throughout the country in order to provide a better cross-section of enrollees, serve demographically diverse populations and provide increased access to cutting edge health care services.

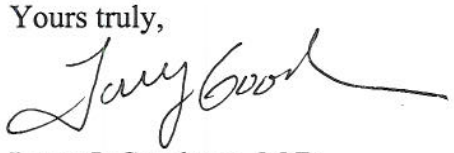
The current approach leaves important basic decisions on clinical trial coverage to the discretion of local Medicare medical directors who need not agree with each other. Along with the general confusion this system creates, there are enormous inefficiencies in negotiating sponsorship agreements and difficulties in serving an increasingly mobile Medicare beneficiary population. A single trial may be determined to have therapeutic intent in one State but may be rejected in a neighboring State. This prejudices sponsors against designing trials that seek to enroll more Medicare beneficiaries because of the frustration in dealing with the regional variations in reimbursement.

This system not only creates frustration within the health care provider community, but it also is confusing to the Medicare beneficiary. We have had experiences reported to us of Medicare beneficiaries who are enrolled in a trial and may have items and services covered by Medicare while in one State but are not covered in another State when the person moves or travels regularly between regions of the country. Because Medicare beneficiaries may be enrolled in a clinical trial for a considerable period of time (as an example, a patient may be enrolled in a cancer clinical trial for several years), the Medicare beneficiary's enrollment may span significant life and living changes that involve receiving treatment in different regions of the country. Medicare beneficiaries typically assume that a Federal program, such as Medicare, is administered similarly throughout the country; it is the unfortunate nature of the Medicare Program's structure that this is not the case. Any actions by CMS to promote consistency would be welcomed by all participants in the health care delivery system.

Knowing that there are limitations on CMS in dealing with the regional deference that is inherent in the Medicare Program, we encourage CMS to devise a process that reviews and treats all clinical trials consistently throughout the country. Clinical trial care is not a matter dependent upon local practice, but is designed to ensure medical research is conducted with integrity and consistency so that maximum knowledge is achieved through clinical trial placement in diverse sections of the country.

We look forward to dialogue on these issues and respectfully submit these comments for your consideration.

Yours truly,



Larry J. Goodman, M.D.
President & Chief Executive Officer

cc: Mark B. McClellan, M.D., Ph.D
Steve E. Phurrough, M.D.

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August 9, 2006

BY ELECTRONIC DELIVERY

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Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mailstop: C1-12-28
7500 Security Blvd.
Baltimore, MD 21244

Re: NCA Tracking Sheet for Clinical Trial Policy (CAG-00071R)

Dear Dr. Phurrough:

The California Healthcare Institute (CHI) welcomes this opportunity to comment on the Centers for Medicare & Medicaid Services' (CMS) Tracking Sheet regarding the development of a Clinical Research Policy (CRP) as a reconsideration of its national coverage decision (NCD) on Medicare coverage of clinical trials.[1] CHI represents the biomedical sector of the California economy and unites more than 250 of California's leading life sciences firms, universities, and private research institutes in support of biomedical science, biotechnology, and pharmaceutical and medical device innovation. California is the global leader in biomedical research and development, with more than one-third of all U.S. biotechnology and medical device firms, turning scientific discoveries into medical products at an unprecedented rate. California firms alone produce more than 20 percent of all medical instruments in the United States and lead the nation in bringing to market frontline treatments and therapies for diseases such as AIDS, breast cancer, stroke, and diabetes.

We strongly believe that clinical evidence is vital to patients, providers, and policy-makers' health care decisions. Our members comprise the various segments of the clinical research system, including the manufacturers that develop new therapies and sponsor research and the universities and research institutions that perform it. CHI members have long demonstrated their dedication to research and innovation. In 2005, California's biomedical industry invested $26 in the development of new products for unmet medical needs, an $11 billion increase over

1 NCA Tracking Sheet for Clinical Trial Policy (CAG-00071R) (hereinafter "Tracking Sheet").

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2003.[2] The average company invested 42 percent of its revenues back into research and development.[3] The clinical research conducted by CHI's members helps patients and physicians understand how medical technology can be used most effectively. We fully endorse the use of evidence obtained from such research to further clinical knowledge and improve medical decision-making.

CHI appreciates CMS' efforts to clarify its criteria on Medicare coverage of clinical trials. We urge CMS to do so in a manner that does not limit beneficiary access to care or render patients, providers, and clinical trial sponsors responsible for significant additional costs. The CRP has the potential to strengthen the clinical trial system in the United States and to thus better enable the various members of the clinical research community to implement and assess new ground-breaking therapies that will prove beneficial to Medicare patients. Accordingly, as CMS develops the CRP, we ask for consideration of our comments and concerns provided herein. CHI separately will comment on the agency's recent "Guidance for the Public, Industry, and CMS Staff on NCDs with Data Collection as a Condition of Coverage: Coverage with Evidence Development (CED)" that was issued on July 12, 2006. We request that CMS evaluate the ramifications that the CRP and the CED policies together may have upon Medicare coverage of clinical trials and beneficiary access to them.

In particular, CHI encourages the permanent inclusion of clinical trials exempt from the investigational new drug application (IND) process in the CRP, as well as urges CMS to develop a process that would allow other research studies to qualify for Medicare coverage. Second, we ask CMS to clarify that the development of the CRP in no way impacts the 1995 HCFA/FDA interagency agreement which now authorizes coverage for routine care cost of IDE trials. Third, we ask that CMS carefully develop any guidelines designed to establish minimum thresholds for Medicare beneficiary participation in clinical trials and take into consideration the challenges of enrolling of such patients in research before establishing any such standards. Fourth, we encourage CMS to develop data collection standards that avoid placing unnecessary burdens upon patients, providers, and clinical trial sponsors. Finally, we ask that CMS clarify that a clinical trial sponsor is not considered a primary payer for certain Medicare-covered medical costs related to the trial where the informed consent document or clinical trial agreement states that the sponsor will pay for certain *uncovered* costs.

Our preliminary comments are set out in more detail below, and we look forward to the opportunity to comment on the proposed CRP.

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2 CHI, 2006 California Biomedical Industry Highlights, available at http://www.chi.org/industry/data.aspx.

3 Id.

I. Inclusion of IND-Exempt Trials and Additional Research Studies

CHI strongly encourages CMS to include IND-exempt trials among those clinical trials "deemed" qualified for Medicare coverage in the CRP. The 2000 NCD lists trials automatically "deemed" to be qualified as covered by Medicare, including trials conducted under an IND reviewed by the Food and Drug Administration (FDA). In addition, IND-exempt drug trials also are considered "deemed" until such time as a qualifying process for these trials was developed. Qualifying criteria for IND-exempt trials have not been established, however, and we ask that IND-exempt trials continued to qualify under the temporary "deemed" status.

IND-exempt trials clearly should be eligible for Medicare coverage. FDA allows exemption of clinical investigations of lawfully marketed drugs in the United States only upon the fulfillment of certain requirements.[4] The exemption applies principally to trials conducted by researchers investigating new uses for marketed drugs in which safety is not at issue and where the research is not sought to support labeling change.[5] FDA even promotes the use of the IND-exempt process for qualifying trials. For instance, FDA has suggested that clinical research for oncology products should employ the IND-exempt process where possible rather than submitting INDs for such products.[6] Research studies conducted through the IND-exempt process have resulted in the post-approval development of many innovative health therapies. Permanent treatment of IND-exempt trials as "deemed" qualified for Medicare coverage will provide more clarity to patients and providers regarding Medicare coverage for routine medical costs.

In addition to adding IND-exempt studies to the list of qualifying trials, CHI urges CMS to develop a qualifying process for other research studies that do not operate under the IND or IND-exempt process. This would replace the self-certification process that never was implemented subsequent to the 2000 NCD. To this end, we encourage CMS to publicize the inter-agency panel findings that were developed for purposes of establishing the self-certification process and to consider these recommendations in developing a similar process in the CRP. We are concerned that removal of the self-certification process would restrict access by Medicare beneficiaries to the various research studies being conducted and could prevent such patients from enrolling in those studies best suited to their medical

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4 21 C.F.R. § 312.2(b); 52 Fed. Reg. 8798, 8801 (Mar. 19, 1987) (noting that "a study of a marketed drug involving an indication contained in the product's approved labeling would be subject to all relevant [IND] requirements" but would be "exempt from IND submission requirements if it met the conditions of § 312.2").

5 48 Fed.Reg. 26720, 26721 (June 9, 1983); *see also* 52 Fed.Reg. 8798, 8799-8800 (Mar. 19, 1987).

6 Food and Drug Administration, "Guidance for Industry, IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer," January 2004, available at www.fda.gov/cder/guidance/6036fnl.htm.

conditions. We believe that development of a process for qualification of research studies that do not fall under the IND or IND-exempt process would allow greater beneficiary access to the array of research trials underway and ensure patient participation is condition-appropriate.

II. Continuation of Medicare's Current Coverage of IDE Trials

Under longstanding regulations, Medicare covers costs in FDA-approved Investigational Device Exemption (IDE) clinical trials involving Category B devices.[7] Since 2004, Medicare also covers routine care costs in IDE trials for Category A devices if the device is used in the diagnosis, monitoring, or treatment of an immediately life-threatening disease or condition.[8] CHI supports this policy, which allows patients to benefit from advanced new devices while also contributing to a growing clinical knowledge base. We ask CMS to continue this policy and confirm that the reconsideration of the clinical trials NCD only serves to expand coverage beyond what Medicare already pays for through its IDE policy.

III. Greater Medicare Beneficiary Participation

CHI endorses CMS' efforts to increase Medicare beneficiary participation in research studies. Development of the CRP has the potential to improve Medicare patient access to clinical trials. We are concerned with CMS' suggestion in the Tracking Sheet, however, that it may set forth guidelines requiring inclusion of a representative sample of Medicare beneficiaries in a Medicare covered clinical trial. We believe that conditioning coverage of such studies upon specific levels of Medicare patient enrollment actually would restrict the availability of clinical trials for Medicare patients by severely limiting the range of trials available for Medicare coverage.

CHI strongly encourages CMS to address the obstacles to the enrollment of Medicare beneficiaries in clinical trials yet also refrain from developing overly restrictive beneficiary enrollment standards in the CRP. Securing participation by Medicare beneficiaries in clinical research is challenging, in part because of trial eligibility criteria as well as trial characteristics. Many Medicare beneficiaries do not meet the eligibility requirements for enrollment into a clinical trial due to factors such as co-morbidities, complications of conditions, and participant age. In addition, clinical trials may impose certain inconveniences such as travel or change in a physician or other care provider that discourage Medicare patients from choosing to enroll in trials. These barriers to participation, inherent in clinical

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7 42 C.F.R. § 405.207(b)(3).

8 42 C.F.R. § 405.207(b)(2).

trials, also have a strong impact upon the representation of rural residents, minorities, and women in clinical studies.

The challenges of enrolling Medicare beneficiaries are especially pronounced in clinical trials involving medical devices. Medical device trials typically enroll a very limited number of patients. In some cases, FDA imposes an age limit or other restrictions on participation in device trials that make it highly unlikely that a Medicare beneficiary could qualify. Any minimum thresholds must recognize the differences between trials involving drugs or biologicals and those trials involving medical devices.

Rigorous requirements regarding beneficiary representation would further restrict beneficiary participation by reducing the number of trials available to those patients eligible and willing to participate. This, in turn, would further limit the availability of evidence related to the Medicare population. In order to provide Medicare coverage to those eligible beneficiaries willing to participate in clinical trials, we urge CMS to develop the CRP in a manner that encourages beneficiary participation without conditioning coverage upon certain levels of Medicare patient representation.

IV. CED and Data Collection

CHI supports CMS' efforts to develop the CRP in conjunction with the agency's recent CED guidance. CHI requests that CMS consider our CED comments in developing the CRP proposed decision memorandum. Generally, we embrace a demanding evidence development process that requires thorough analysis of a disease and its potential therapies. CHI appreciates CMS' recent statements that CED will be used sparingly and in order to expand access to technologies and treatments for Medicare beneficiaries. With respect to the CRP, however, we remain greatly concerned about any obligations imposed on clinical trial sponsors to collect data. We strongly encourage CMS to leave the imposition of such standards to FDA or, at a minimum, adopt standards with the least possible burden upon patients, providers, and clinical trial sponsors.

Stringent data collection obligations could result in significant administrative and financial burdens for both sponsoring manufacturers as well as participating patients and providers. It is essential that CMS minimize these costs to the greatest extent possible. Additional data collections requirements are particularly challenging for smaller companies. Medical devices, as well as biotechnology therapies, often are developed by companies that may have only one or two products on the market, if any. These companies do not have the ability to spread additional and unanticipated data collection and other requirements across many trials that larger companies may have.

Increased clinical trial costs also may lead to higher costs for patients. If this is the care, many patients may opt to participate in less expensive programs of care instead of the most medically appropriate option, potentially the Medicare-covered trial. CMS also must consider the cost to providers in establishing data collection obligations. Physicians participating in clinical trials donate many services that are not reimbursed by trial sponsors or by Medicare, such as evaluation of patient eligibility, data collection, and drug administration. Imposing increased costs upon physicians due to CED and data collection will reduce the ability of many physicians to donate time and resources to important clinical research.

We strongly encourage CMS to determine when additional data collection is vital to Medicare covered clinical trials by carefully considering whether the value of the information sought warrants the administrative and financial costs of collection. In its calculation, CMS should take into account the effect any such costs may have upon participation in clinical trials by beneficiaries and providers and seek to ensure that research resources are used as efficiently as possible. One way that CMS may seek to ensure that the value of the information collected outweighs the cost of its collection is to consult the relevant stakeholders of the covered clinical trial. When additional data collection is justified, we encourage CMS to work with the sponsor and trial site to outline the data collection needs at the outset. We also caution that CMS' appropriate role in the clinical trial process is as a payer, and we encourage CMS to avoid duplicating tasks already granted to FDA.

In the Tracking Sheet, CMS also indicates that the CRP will attempt to "[c]larify how items /services that do not meet the requirements of 1862(a)(1)(A) but are of potential benefit can be covered in clinical research studies as an outcome of the National Coverage Determination process."[9] We ask that CMS include this inquiry in the CED guidance, and we welcome the opportunity to address this issue in our comments on to that document.

V. The Role of Medicare as a Payer

CHI asks CMS to clarify that a clinical trial sponsor, study site, or investigator does not become a primary health plan for purposes of the Medicare Secondary Payer rules when the sponsor agrees in an informed consent document or clinical trial agreement to pay for uncovered costs for medical services resulting from a trial-related illness or injury.

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9 NCA Tracking Sheet for Clinical Trial Policy (CAG-00071R)

Medicare pays for items and services that are reasonable and necessary for the treatment of illness or injury,[10] including those items and services needed to treat complications arising from participation in a clinical trial. The 2000 NCD states that such items and services are part of the routine costs covered by Medicare in a clinical trial.[11] Medicare regulations also make clear that Medicare pays for complications arising from clinical trials involving the use of medical devices.[12]

Under the Medicare Secondary Payer (MSP) rules, Medicare payment is not available where payment for an item or service is available under a "primary plan."[13] Under the statute, a "primary plan" includes group health plans, worker's compensation laws or plans, automobile or liability insurance policies or plans (including a self-insured plan), and no fault insurance.[14] A clinical trial sponsor is not a primary plan under the MSP statute. Moreover, clinical trial sponsors typically offer to pay for expenses relating to a complication arising from the trial where these expenses are not otherwise covered. Institutional Review Boards typically require such language as part of a clinical trial agreement or informed consent document. Where such a statement in the clinical trial agreement or informed consent document has the effect of precluding Medicare payment, the result is that Medicare beneficiary participation in the clinical trial is restricted. Clinical trial sites are reluctant to enroll Medicare beneficiaries where Medicare payment is uncertain or billing problems may arise. CHI urges CMS to clarify that a sponsor's offer to pay for uncovered costs arising from complications does not render the sponsor a "primary plan" for purposes of the MSP provisions. This will provide clinical trial sites the reassurance needed to run trials that include Medicare patients and will allow beneficiaries greater access to medically appropriate clinical studies.

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10 42 U.S.C. §§ 1395(d) (entitlement to have payment made for inpatient hospital services), 1395k(a)(1) (entitlement to have payment made for medical and other health services), 1395y(a)(1)(a) (exclusion for items that are not reasonable and necessary for treatment of illness or injury).

11 Medicare Coverage, Clinical Trials, Final National Coverage Decision, *available at* http://www.cms.hhs.gov/coverage/8d2.asp.

12 42 C.F.R. § 405.207(b). The regulation calls for payment even when the device itself is unapproved, making clear that coverage also is compelled where the device is an approved one.

13 42 U.S.C. § 1395y(b)(2)(A).

14 *Id.* In the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Congress amended the definition of "primary plan" to state that "[a]n entity that engages in a business, trade, or profession shall be deemed to have a self-insured plan if it carries its own risk (whether by a failure to obtain insurance, or otherwise) in whole or in part." 1862(b)(2)(A).

VI. Conclusion

CHI appreciates the opportunity to comment on CMS' efforts to developed a proposed CRP. We look forward to commenting on the proposed CRP once it is issued. We hope that our recommendations are useful to CMS in developing a proposed CRP that both provides Medicare coverage for clinical trials in a predictable manner and improves Medicare beneficiary access to cutting-edge therapies. In particular, we ask that CMS:

- expressly include IND-exempt clinical trials as deemed,
- continue Medicare's policy of covering IDE trials,
- develop a process for other research studies to qualify for Medicare coverage;
- carefully craft guidance related to the representation of Medicare beneficiaries in Medicare-covered trials to encourage greater beneficiary participation without restricting the availability of clinical trials to these patients;
- devise data collection standards to fulfill CMS' specific goals while minimizing the burdens imposed on patients, providers, and clinical trial sponsors; and
- clarify that a clinical trial sponsor is not acting as a primary payer for certain medical costs simply by offering in an informed consent document to pay for certain uncovered costs.

We look forward to working with CMS as it develops this policy, and and would be pleased to have the opportunity to meet with you to discuss these comments in more detail. If we can be of any assistance, please contact Todd Gillenwater at 858-551-6677. Thank you for your attention to this important matter.

Sincerely,

David L. Gollaher, Ph.D
President & CEO

cc: Leslye K. Fitterman
Tamara Syrek Jensen

From: Jo Leen Walsh [jwalsh@ucsamd.com] on behalf of Laman Gray [LGray@ucsamd.com]
Sent: Wednesday, August 09, 2006 3:25 PM
To: FITTERMAN, LESLYE K. (CMS/OCSQ)
Subject: 310.1 - National Coverage Decision on Clinical Trial Policy (CAG-00071R)

To effectively evaluate the viability of any clinical study, the ability to benchmark results against other devices is essential to determine appropriateness of care, funding and overall effectiveness of the device. The industry standard, in my opinion, should require enrollment in the clinical trial registry.

Clinical trials which are currently non-covered by CMS, should be considered for reimbursement at the time a device receives PMA or HDE approval. Any device receiving HDE approval has withstood the scrutiny of the FDA which allows Medicare beneficiaries to receive care that may have a health benefit. Since the vast majority of payors follow the reimbursement guidelines established by CMS, it is critical that CMS set this precedent. If this is not done, the clinical trial will not yield an adequate number of enrollees and the trial will not fulfill its mission.

Laman A. Gray, Jr., M.D.

Professor of Surgery

Director, Division of Thoracic

and Cardiovascular Surgery

University of Louisville

Louisville, KY

502-561-2180

From: CMS CAGInquiries
Sent: Wednesday, August 09, 2006 10:22 AM
To: FITTERMAN, LESLYE K. (CMS/OCSQ)
Subject: FW: Medicare support clinical trials

From: T-Force Imaging Research [mailto:tforceimagingresearch@comcast.net]
Sent: Tuesday, August 08, 2006 6:09 PM
To: CMS CAGInquiries
Subject: Medicare support clinical trials

To Whom it may concern:

In the general interest of science and public wealthfare, we support and strongly urge that CMS continues to support Medicare coverage for clinical trials.

This support provides a means to encourage seniors to participate in studies. The geriatric population is growing rapidly and ways to evaluate their needs and circumvent disease processes must be promoted. 78 million adults are a few short years away from becoming part of the geriatric population in this country. We are at a critical junction to obtain studies whose results can be used as interventions and to ameliorate any suffering of this group whose welfare will be sustained by a smaller subsequent generation.

The current healthcare industry -- which is already taxed considerably in terms of manpower and available dollars -- will not suffice to support this shift without the advancement of science and technology to provide point-of-care solutions, streamline costs, cut man hours, and provide a continuum of care that can hold up under the burden of large numbers of elderly patients.

We support any amendment or proposal that supports the continuation of studies of the geriatric population, and we discourage the withdrawal of any formal support from Medicare studies, as we will all one day join the ranks of the elderly.

Very Sincerely,
Mary Meldrum
Owner, Vice President
T-Force Imaging Research

THE AMERICAN SOCIETY OF HEMATOLOGY
1900 M Street, NW, Suite 200, Washington, DC 20036 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

August 9, 2006

Mark McClellan, MD, PhD
Administrator
Center for Medicaid and Medicare Services
7500 Security Blvd.
Baltimore, MD 21244

Re: **Clinical Trial Policy Reconsideration (CAG-00071R)**

Dear Dr. McClellan:

The American Society of Hematology (ASH) represents approximately 10,000 hematologists in the United States who are committed to the treatment of blood and blood-related diseases. ASH members include hematologists and hematologist/oncologists who render blood and bone marrow transplant (BMT) services to Medicare and Medicaid beneficiaries. ASH appreciates the opportunity to comment on the reconsideration of the Clinical Trial Policy.

The Centers for Medicare and Medicaid Services (CMS) national coverage decisions regarding BMT therapies do not compare favorably to national standards of care for some diseases, such as myelodysplasia and multiple myeloma. Such coverage decisions may create access issues for beneficiaries seeking treatment, particularly when that treatment would be delivered via a clinical trial.

ASH has comments on several of the issues outlined in the reconsideration.

- **Number Four (Clarify the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials):** Investigators must understand the services that constitute routine care as opposed to those performed only to carry out the clinical trial. ASH and other organizations within the BMT community could provide guidance to CMS, sponsoring organizations, and investigators to clarify the distinction.

- **Number Eight (Clarify how items/services that do not meet the requirements of 1862 (a)(1)(A) but are of potential benefit can be covered in clinical research studies as an outcome of the National Coverage Determination Process)** and **Number Nine (Clarify whether and under what conditions an item/service non-covered nationally may be covered in the context of clinical research to elucidate the impact of the item or service on health outcomes in Medicare beneficiaries):**

ASH considers both items as pertaining to potential expansion of coverage in the context of clinical research. ASH believes that there are important services that may not yet have enough evidence based practice to be a covered benefit, but could still hold significant value to the patient. Allogeneic BMT for multiple myeloma is an important example. A high-priority trial funded by the National Institutes of Health (NIH) conducted through the BMT Clinical Trials Network is addressing the role of allogeneic BMT in treating multiple

myeloma. This important study is currently excluded as a Medicare benefit because allogeneic BMT for myeloma is not a covered benefit nationally. ASH strongly supports coverage for deemed National Cancer Institute (NCI) studies as an important component for access both to current BMT therapy, and advancement in the field. We believe that Medicare coverage of these additional (currently) non-covered benefits will help ensure the best possible care available. Additionally, regulatory changes should be implemented to allow consensus conferences between the granting agency and CMS to determine coverage in the context of clinical research.

ASH strongly requests CMS to consider the potential impact their reconsideration of clinical trial policy will have on the Medicare population. Not covering efficacy studies has resulted in a lack of crucial efficacy data. Non-coverage policy leads to fewer Medicare beneficiaries undergoing needed BMT services. ASH would be pleased to work with CMS on developing clinical trial policy regarding BMT that may improve access to important therapies for Medicare beneficiaries while still capturing relevant data. Please contact Pamela Ferraro, ASH Practice Advocacy Manager, at pferraro@hematology.org or 202-776-0544 for more information.

Sincerely,

Samuel M. Silver, MD, PhD
Chair, ASH Subcommittee on Reimbursement
ASH CPT/RUC Representative

Richard I. Smith
SENIOR VICE PRESIDENT
POLICY, RESEARCH AND STRATEGIC PLANNING

PhRMA

August 9, 2006

Leslye K. Fitterman, Ph.D
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mailstop: C1-09-06
7500 Security Blvd.
Baltimore, MD 21244

Re: First Reconsideration of Clinical Trial Policy (CAG-00071R)

Dear Dr. Fitterman:

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates this opportunity to comment on reconsideration of the current national coverage decision (NCD) on Medicare's Clinical Trial Policy. This reconsideration was initiated by the Centers for Medicare and Medicaid Services (CMS) on July 10.

PhRMA is a voluntary, nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies. Our members are devoted to discovering new medicines that allow patients to lead longer, healthier, and more productive lives. PhRMA member companies invested approximately four-fifths of the overall biopharmaceutical company research and development expenditures of $51.3 billion in 2005. Through this investment, PhRMA's member companies play a leading role in discovery of new therapies and advancement of scientific and clinical knowledge.

Since its finalization in 2000, CMS' policy of providing Medicare coverage of the costs of routine care for individuals in clinical trials has provided an important tool to encourage beneficiary enrollment in clinical research on promising interventions.

As CMS reconsiders this NCD, it should do so with an overarching goal of maintaining a policy that is patient-centered. This means supporting broad beneficiary access to promising interventions in clinical research. It is with this goal in mind that we offer comments as the agency initiates consideration of potential policy changes.

Specific Comments

1) Goals of the policy:

The current policy was implemented to respond to an important beneficiary need – removing potential policy barriers to access to promising interventions in clinical research – and, as stated above, this patient-centered goal must remain central. The text in proposed goal 2 of CMS' tracking sheet (fostering "research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies") potentially could broaden the scope of the policy well beyond the goal of supporting patient access to promising new therapies in clinical trials. While this type of research can generate findings that are of benefit at a variety of levels (e.g., societal, payer, and clinical), it often is not directly related to the central goal of the current policy -- supporting care of patients in a clinical protocol to ensure they have access to promising and potentially lifesaving interventions. If CMS develops policy in this area, it should clarify how it supports the overarching Medicare goal of improving beneficiary access to promising interventions that are still in clinical research.

2) Future Rulemaking:

CMS states in the tracking sheet that meeting the goals it outlines "will require some clarifications to the current Clinical Trial Policy and may require additional regulatory changes." To the extent CMS believes additional regulatory changes are necessary, the agency should provide additional details in its draft decision memorandum.

3) Local Coverage:

CMS should maintain language in the current NCD policy that assures beneficiaries and providers that "[t]his policy does not withdraw Medicare coverage for items and services that may be covered according to local medical review policies . . ."[1] Providing the option of local coverage outside of the confines of a research protocol is important to ensuring beneficiaries have timely access to medically appropriate interventions such as off-label uses of anticancer therapies. This language also should be updated to reflect the transition from local medical review policies to Local Coverage Decisions.

4) IND-Exempt Trials:

In its tracking sheet, CMS states that in its revised policy it wants to "[c]larify the scientific and technical roles of Federal agencies in overseeing IND Exempt trials . . ." Under the current Clinical Trial Policy, certain IND-exempt trials are deemed

[1] "Routine Costs in Clinical Trials," §310.1, Medicare National Coverage Determinations Manual (CMS Pub. 100-03).

automatically qualified as reimbursable trials until "qualifying criteria are developed and [a specified] certification process is in place."[2] Because these criteria were never finalized, IND-exempt trials have remained automatically deemed as reimbursable under the current policy. PhRMA encourages CMS to maintain coverage of IND-exempt trials. These trials often are initiated by clinical investigators to conduct further research of treatments outside of sponsor-run protocols. These trials are carefully regulated by FDA, and it is important to maintain Medicare coverage for them in the revised national coverage policy. In addition, in light of existing regulation of IND-exempt trials, comprehensive federal regulatory oversight already is in place, and a national coverage decision is not the appropriate mechanism to modify this regulatory framework.

5) Criteria and process for covering costs of clinical research:

PhRMA strongly supports CMS' goal of clarifying "the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials." Under the current policy, sponsors and investigators often are reluctant to seek reimbursement of routine costs of care because it is not clear exactly which costs qualify and there is not an adequate mechanism for seeking clarification from the agency.

Giving investigators and patients greater clarity in these areas will foster increased Medicare beneficiary participation in clinical trials. We would be pleased to work with the agency and other stakeholders toward this goal.

CMS also could further the goal of encouraging Medicare beneficiary enrollment in clinical trials by clarifying the types of trials that qualify. In particular, further clarification of the "desirable characteristics" of trials identified in the existing policy would give investigators greater assurance that qualifying research costs will be covered by Medicare.

6) Coverage with Evidence Development:

In CMS' revised guidance document on "Coverage with Evidence Development" (CED), released July 12, the agency links one "arm" of CED, "Coverage with Study Participation," to the revised clinical research policy that will be developed through this pending NCD reconsideration.[3] Specifically, the CED guidance states that "CMS will only provide payment for clinical research that meets the standards of a qualified trial as will be outlined in the revision of the Clinical Trial Policy."

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[2] "Routine Costs in Clinical Trials," §310.1, Medicare National Coverage Determinations Manual (CMS Pub. 100-03).

[3] "Guidance for the Public, Industry, and CMS Staff -- National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development (July 12, 2006), https://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8.

Though PhRMA will comment separately on the revised CED guidance, we urge CMS to clearly articulate in both documents the means through which Medicare will establish clinical research standards and direct or support clinical research. For example, both CSP and the revised clinical research policy (as the latter is depicted in the reconsideration tracking sheet) rely for their statutory authority on sections 1862(a)(1)(E) and 1142 of the Social Security Act. The effect of drawing on these two provisions is to establish as a framework for clinical research certain programs under the aegis of the Agency for Healthcare Research and Quality (AHRQ). We urge CMS to specify more clearly the role of AHRQ in carrying out Medicare's clinical research policy, as well as the types of public-participation opportunities that will be available as AHRQ discharges its role.

7) Research Requirements:

CMS should clarify the issue of developing criteria to "assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries, by demographic and clinical characteristics." If the agency sets an unrealistic threshold for achieving a representative sample of beneficiaries, it could have the effect of creating a new barrier to enrollment in clinical trials. It is also unclear how this would be enforced in practice. For example, will a threshold number of beneficiary enrollees be established at the start of the study in order for the study to qualify for coverage? If it is not possible to meet that number over the time period of the study, which may be years, how would coverage be handled for those who have already enrolled and may have already had some aspects of care reimbursed?

8) NIH clinical trials registry website:

In the tracking sheets CMS expresses its interest in devising "a strategy to ensure that Medicare covered clinical studies are enrolled in the National Institute of Health (NIH) clinical trials registry website."

PhRMA is committed to timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing. As such, PhRMA sponsors a database, www.clinicalstudyresults.org, to help make results more transparent and user-friendly to physicians. This effort is separate from and complementary to NIH's clinical trials registry web site.

As you know, submission of certain pharmaceutical trials to NIH's clinical trials registry is mandatory, while submission of all other trials is voluntary. As CMS considers changes in this area, it should pay particular attention to the potential interaction of these policies. We look forward to providing further input on this issue in comments on the draft coverage memo.

PhRMA appreciates this opportunity to provide initial input on CMS' reconsideration of its policy on coverage of costs of clinical trials. As this reconsideration progresses, we look forward to working with CMS and to commenting in greater detail when the agency's draft coverage decision is released.

Sincerely,

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BY ELECTRONIC DELIVERY

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Re: Comments on the Coverage with Evidence Determination Draft and on the NCA Tracking Sheet for Clinical Trial Policy (CAG-0071R)

Dear Administrator McClellan:

Novartis Pharmaceuticals Corporation appreciates this opportunity to comment on the above-referenced draft policies. The first is the guidance for national coverage determinations with data collection as a condition of coverage, known as "Coverage with Evidence Development" (CED), issued by the Centers for Medicare and Medicaid Services (CMS) on July 12, 2006. Novartis is interested in working with CMS to accept voluntary data registries run by outside professional organizations as a data collection tool for assistance in making coverage decisions. In this comment, Novartis focuses specifically on the application of CED to new therapies for age-related macular degeneration (AMD). The second is CMS' Tracking Sheet regarding the development of a Clinical Research Policy (CRP) as a reconsideration of its national coverage decision (NCD) on Medicare coverage of clinical trials (CAG-00071R). Novartis supports CMS' desire to cover routine clinical costs for Medicare beneficiaries in approved clinical trials. Novartis believes that this will ultimately increase participation in clinical trials, and both speed innovation and increase access to innovative therapies. We do urge CMS, however, to deem industry-sponsored trials to meet criteria 5 on the list of "desirable characteristics" for clinical trials, which requires that the trial be sponsored by a credible organization capable of implementing the trial successfully.

The Novartis Group is a global leader in pharmaceutical research, development, and manufacturing in multiple therapeutic areas, including oncology, ophthalmics, transplantation, and cardiovascular disease. Novartis has a significant research interest in the CED guidance because it is currently involved in marketing Visudyne (verterporfin for injection) for the treatment of AMD. Novartis has already developed a comprehensive patient data registry for AMD therapy with the goal of enhancing clinical management of AMD patients through the collection and development of high-quality outcome data. Novartis would like to collaborate with CMS and other stakeholders to expand the registry and to maximize its clinical impact.

Finally, Novartis strongly believes that any registry data that is made available to the public should be de-identified and protect patient privacy.

CED Relies on the Stakeholder Initiative and Participation

Since CMS issued its draft guidance on CED in April 2005, the agency and stakeholders have gained experience implementing several CED coverage decisions, including data registries for implantable cardiac defibrillators (ICD), positron emission tomography (PET) for oncologic indications, and a clinical trial for off-label uses of certain anti-cancer agents. CMS's revised guidance document reflects its experience with these early CED initiatives. In particular, the agency has made clear that that it does not intend to fund, "routinely develop, oversee, or maintain these databases or registries that contain information about provision of an item or service." As a result, most of the logistical, administrative and financial support for data registries will have to come directly from stakeholders.

Novartis believes that the CMS guidance affords an important opportunity to expand the current CED framework to include data registries sponsored by independent third parties. Indeed, as an alternative to agency-funded and administered data collection, CMS encourages stakeholders—including manufactures, healthcare providers and facilities, professional societies, foundations, and health plans—"to work together to provide additional support for data collection efforts." The guidance further recommends that in order "to ally the cost of data collection," whenever feasible CED should "take place in the context of an existing data system."

Novartis proposes to do exactly this by collaborating with manufacturers, patient groups, professional societies, and CMS to expand the scope on its existing InSight Registry and by conforming the registry's data collection process to CED-sanctioned principles.

Expanded Data Collection for AMD

Novartis would like to work with CMS and other stakeholders to develop an AMD data registry that is fully consistent with CMS policy guidance on CED. The AMD data registry would build on the current industry-sponsored InSight Registry, which could be modified to meet the evidence needs of CMS, other payers, clinicians, and patients. The AMD Registry would be supported by major companies involved in research and development of AMD treatments, as well as the broader clinical community and patients' organizations. Operational support, governance, oversight, and data collection and analysis would be provided by an independent, disinterested organization.

In particular, CMS has stated that it will only accept data that can inform the agency's determination of whether a given item or service is reasonable and necessary for purposes of Medicare coverage and which was collected subject to "qualified scientific oversight, tested and validated data collection methods; adequate patent safety and monitoring; qualify assurance and data protection and appropriate human subject projects." Novartis understands that AHRQ is drafting a report on data registries, and urges that CMS affords the public an opportunity to comment on the standards for registry design. Novartis looks forward to continuing to work with CMS and other stakeholders in the coverage of age-related macular degeneration. The principles in the AHRQ report will be helpful for designing and implementing the expanded AMD registry.

Background on The InSight Registry

The clinical management of AMD is undergoing revolutionary changes. The emergence of new drugs and treatment strategies has shifted the ultimate goals of therapy from merely preventing vision loss to actually restoring visual acuity (VA). The increasing availability of multiple therapeutic options that work through a variety of biologic mechanisms have raised important new questions for practitioners about the optimal sequence and combination of treatments. Retinal specialists are keenly interested in experimenting with new approaches to treatment for the benefit of their elderly patients. Providers, payers, patients, and manufacturers share the goal of continuing to develop high quality evidence on the benefits, risks, and costs of alternative treatment regimens for AMD.

The InSight Registry is an observational web-based database involving 150 community practices and academic centers and was launched by Novartis in 2005. The design of the registry was guided by a special Oversight Committee comprised of leading retina specialists. InSight collects data for all pharmaceutical treatments for AMD actually used by the participating practices, regardless of whether the treatments are in- or out-of-label and does not employ patient exclusion criteria. The purpose of the InSight Registry is to identify and to bridge knowledge gaps in real world patterns of care. To that end, it collects outcomes data on alternative treatment regimens, including combination therapies chosen by the practitioners, as well as data on vision-related quality of life and function measurements.

Specifically, the registry collects data on each patient's clinical condition (including legion type, size and location, as well as VA); treatment regimen (including initial treatment, re-treatment, and changes in therapy); drug choices (including the clinician's basis for a particular therapeutic regimen, doses and route of administration); imaging techniques (such as fluorescein angiography (FA), ocular coherence tomography (OCT), and indocyanine green angiography (ICGA)); and clinical outcomes data.

Registry Data Should be De-identified to Protect Patient Privacy

Novartis wishes to place special emphasis on the importance of vigorously protecting the privacy of patients whose data is submitted to CED registries. Novartis supports the public dissemination and use of outcomes data but believes that registries must incorporate protections of patient confidentiality. In the guidance document CMS details the circumstances under which the public may gain access to registry data by entering into a data use agreement with CMS. Novartis strongly believes that any data released to the public should be de-identified to protect patient confidentiality. Registries that do not de-identify patient data risk limiting the number of patients and physicians who agree to participate in a study. CMS should issue additional detailed guidance on the protection of patient privacy in the context of disseminating registry data.

Coverage of Clinical Trials is Another Important Aspect of Evidence Generation

Novartis is pleased that CMS has begun to finalize its policy surrounding the June 7, 2000, executive memorandum concerning coverage of routine patient care costs associated with Medicare beneficiary participation in clinical trials. Coverage of routine clinical costs for Medicare beneficiaries in approved clinical trials will have multiple beneficial effects: 1) it should help increase Medicare beneficiary participation in clinical trials - given that Medicare beneficiaries are often underrepresented in clinical trials, this should help increase the data needed to understand the benefits of various medical interventions in the senior population; 2) it will help speed access to new and innovative medical

interventions to the Medicare populations; and, 3) it will help increase innovation in the development of medical procedures, drugs, and devices used to treat conditions affecting the Medicare population.

Our one comment concerns the "desirable characteristic" of the clinical trials (number 5 on the list): "The trial is sponsored by a credible organization…capable of executing the proposed trial successfully." We urge CMS to include industry-sponsored trials under this characteristic (provided, of course, the specific trial meets the other needed characteristics). Trials conducted under the direction of industry are generally well-designed, monitored, and subject to expert data analysis. Industry-sponsored trials often allow for the enrollment of larger populations than trials conducted by individuals or small groups. Generally speaking, the only trials that can compare in total resources are those sponsored by government entities (which are already "deemed") and academic-sponsored trials (although here funding constraints often necessitate academic centers to turn to government or industry funding).

In addition, we urge CMS to allow on-label post-marketing trials as well as non-registration trials designed to study off-label uses of drugs. By allowing industry-sponsored trials to be deemed eligible for coverage of routine clinical care costs, CMS will truly be aiding in increased access to therapies for Medicare beneficiaries and also supporting the development of new, innovative therapies.

We look forward to working with you as CMS implements these new coverage policies.

Very truly yours,

Bonnie Washington

cc: Steve Phurrough, M.D. (Director, Coverage and Analysis Group)
Ross Brechner, M.D., M.S., M.P.H.

CMS Seeks Comments on Reconsideration of the National Coverage Decision for Clinical Trial Policy

Thank you for inviting comment on the reconsideration by CMS of its national coverage decision on the Clinical Trial Policy. We appreciate the opportunity to provide input because this reconsideration will have important direct and indirect repercussion for Health Plans and for the membership they serve.

The proposed Clinical Research Policy has three stated goals:

1) **to allow Medicare beneficiaries to participate in research studies;**
2) **to encourage the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies in the Medicare population, thus improving the quality of care that Medicare beneficiaries receive; and,**
3) **to allow Medicare beneficiaries to receive care that may have a health benefit, but for which evidence for the effectiveness of the treatment or service is insufficient to allow for full, unrestricted coverage."** See **NCA Tracking Sheet for Clinical Trial Policy (CAG-00071R)**

The present Clinical Trial Policy from 2000 directs Medicare to pay for the routine costs of beneficiaries enrolled in certain clinical trials and requires the trials to be approved by CMS prior to reimbursement. Each of these trials begins with a basic question: "Do the potential benefits of the proposed service outweigh the potential harm?" The goal of each trial is to learn whether or not a service works and whether or not it is safe. Mayo Clinic has stated that about 20 percent of treatments successfully make their way through the three clinical trial phases and are ultimately approved, becoming standards of care. (MayoClinic.com Tools for healthier lives). In other words, 80% of clinical trials do not result in approved therapies, either falling short in demonstrated benefit, safety or both. Thus, participants in these trials can be said to be making a sacrifice because research trials are geared toward benefiting future patients while those who participate in early studies of a treatment may not personally benefit at all or worse, may be harmed. We are concerned that a relaxation of scientific rigor underlying Medicare-supported research studies could have the unintended consequence of lowering the track record of 20% of treatments that are ultimately approved and increasing the risk to research study participants.

Ten issues were identified that have surfaced since the Clinical Trial Policy was implemented. Number eight is **"Clarify how items/services that do not meet the requirements of 1862(a)(1)(A) but are of potential benefit can be covered in clinical research studies as an outcome of the National Coverage Determination process;"**

1862(a)(1)(A) states that no Medicare payment shall be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury. The proposal that by merely demonstrating the potential for benefit, items or services could be covered despite not meeting the requirement of 1862(a)(1)(A) invites a serious

degradation of an evidence-based approach to coverage determinations. When coverage determinations have strayed from an evidence-based rationale, there have been unfortunate outcomes. For example, the decision to mandate coverage for bone marrow transplants for women with breast cancer appears to have resulted in a failure to improve survival in the recipients while exposing them to the toxicities related to this aggressive and costly treatment. Prior to learning that several clinical trials failed to show a survival benefit, there was the "potential for benefit."

We welcome CMS scrutiny of the current Clinical Trial Policy because we believe there are opportunities to benefit our Members that should be supported and pursued.

1. We would like to see a priority placed on isolating which particular patients benefit from drugs or proposed therapies and which do not. An example of this done well is Herceptin (tratuzumab). Women with breast cancer positive for the Her-2/neu gene are candidates for Herceptin and are most likely to benefit from the treatment. Those with breast cancer negative for Her-2/neu should not receive Herceptin because they would not be expected to benefit and would thus avoid the toxicities related to the treatment. Unfortunately, once a therapy has shown benefit for patients suffering from a disease state, there isn't the pursuit to find the subset of patients who most benefited and those who didn't benefit. This sort of inquiry usually takes place only when a therapy fails to demonstrate a significant benefit across a broader group of patients (e.g. Iressa).

2. We see the need for more active pursuit of reliable biological markers of disease and their use in defining the treatment population.

3. There is an important need for long-term data. This would allow for meaningful clinical endpoints such as overall survival instead of the sometimes misleading surrogate markers that are used. This would also permit enhanced discovery of toxicities related to treatment (e.g. Vioxx).

Thank you for the invitation to comment on the Reconsideration of the Clinical Trial Policy.

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